

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549**

Form 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2022

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission file number 001-37813

SYROS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

35 CambridgePark Drive, 4th Floor
Cambridge, Massachusetts
(Address of principal executive offices)

45-3772460
(I.R.S. Employer
Identification No.)

02140
(Zip code)

(617) 744-1340

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Class
Common Stock, \$0.001 par value

Trading Symbol
SYRS

Name of Exchange on Which Registered
Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act:
None.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

☐

Non-accelerated filer

☒

Accelerated filer

☐

Smaller reporting company

☒

Emerging growth company

☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to § 240.10D-1(b). ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

As of June 30, 2022, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates was \$55,740,050 based on the last reported sale price of such stock on the Nasdaq Global Select Market as of such date.

Portions of the registrant's definitive proxy statement for its 2023 Annual Meeting of Stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2022, are incorporated by reference into Items 10, 11, 12, 13 and 14 of Part III of this Annual Report on Form 10-K. As of February 27, 2023, the registrant had 20,300,419 shares of Common Stock, \$0.001 par value per share, outstanding.

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Cautionary Note Regarding Forward-Looking Statements and Industry Data

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management and expected market growth are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. The forward-looking statements and opinions contained in this Annual Report are based upon information available to us as of the date of this Annual Report and, while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information.

These forward-looking statements include, among other things, statements about:

- our plans to initiate and expand clinical trials of our product candidates and our expectations for the timing, quantity and quality of information to be reported from our clinical trials of tamibarotene, SY-2101 and SY-5609;
- our planned clinical trials for our product candidates, whether conducted by us or by any collaborators, including the timing of these trials and of the anticipated results;
- our ability to discover and develop compounds suitable for clinical development and the timing for designation of future development candidates;
- our ability to replicate in any clinical trial of one of our product candidates the results we observed in preclinical or earlier clinical studies of such product candidate;
- our plans to research, develop, seek approval for, manufacture and commercialize our current and future product candidates;
- our plans to develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with our products and product candidates;
- our ability to enter into, and the terms and timing of, any collaborations, license agreements, or other arrangements;
- whether a drug candidate will be nominated to enter into investigational new drug application-enabling studies under our sickle cell disease collaboration with Global Blood Therapeutics, Inc., or GBT, whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U.S. co-promotion option under the GBT agreement;
- whether our target discovery collaboration with Incyte Corporation, or Incyte, will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the Incyte collaboration will ever be paid;
- the potential benefits of any collaboration;
- developments relating to our competitors and our industry;
- the impact of government laws and regulations;
- the timing of and our ability to file new drug applications and obtain and maintain regulatory approvals for our product candidates;

- the rate and degree of market acceptance and clinical utility of any products for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position and strategy;
- our ability to identify additional products or product candidates with significant commercial potential;
- our expectations related to the use of our current cash, cash equivalents and marketable securities and the period of time in which such capital will be sufficient to fund our planned operations;
- our estimates regarding expenses, future revenue, capital requirements and need for additional financing; and
- general economic conditions, including inflation, recession risk and increasing interest rates.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. New risks and uncertainties emerge from time to time, and it is not possible for us to predict all risks and uncertainties that could have an impact on the forward-looking statements contained in this Annual Report.

We have included important factors in the cautionary statements included in this Annual Report that could cause actual results or events to differ materially from the forward-looking statements that we make, particularly the factors discussed below under the heading “Risk Factor Summary,” and the risk factors detailed further in Item 1A, “Risk Factors” of Part I of this Annual Report and in our Securities and Exchange Commission reports filed after this Annual Report. In particular, the extent to which the COVID-19 pandemic continues to impact our operations and those of the third parties on which we rely will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the pandemic, additional or modified government actions, and the actions that may be required to contain the coronavirus or treat its impact. COVID-19 has and may continue to adversely impact our operations and workforce, including our discovery research, supply chain and clinical trial operations activities, which in turn could have an adverse impact on our business and financial results.

Our forward-looking statements also do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures or investments that we may make or enter into.

This report also includes statistical and other industry and market data that we obtained from industry publications and research, surveys, and studies conducted by third parties as well as our own estimates. All of the market data used in this report involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys, and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our drug candidates include several key assumptions based on our industry knowledge, industry publications, third-party research, and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

You should read this Annual Report completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Risk Factor Summary

Investment in our securities involves risk. You should carefully consider the following summary of what we believe to be the principal risks facing our business, in addition to the risks described more fully in Item 1A, "Risk Factors" of Part I of this Annual Report and other information included in this Annual Report. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations.

If any of the following risks occurs, our business, financial condition, and results of operations and future growth prospects could be materially and adversely affected, and the actual outcomes of matters as to which forward-looking statements are made in this report could be materially different from those anticipated in such forward-looking statements.

- We have incurred significant losses since inception, expect to incur significant and increasing losses for at least the next several years, and may never achieve or maintain profitability.
- We will need substantial additional funding to execute our operating plan and continue to operate as a going concern, and if we are unable to raise capital on favorable terms, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.
- Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.
- In the near term, we are dependent on the success of tamibarotene, SY-2101 and SY-5609. If we are unable to initiate or complete the clinical development of, obtain marketing approval for or successfully commercialize tamibarotene, SY-2101 or SY-5609, either alone or with a collaborator, or if we experience significant delays in doing so, our business could be substantially harmed.
- If clinical trials of any product candidates that we, or any collaborators, may develop fail to satisfactorily demonstrate safety and efficacy to the U.S. Food and Drug Administration, or the FDA, and other regulators, we, or any collaborators, may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of these product candidates.
- Adverse events or undesirable side effects caused by, or other unexpected properties of, product candidates that we develop may be identified during development and could delay or prevent their marketing approval or limit their use.
- We rely on third parties to conduct our clinical trials and certain aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including by failing to meet deadlines for the completion of such trials, research or testing.
- The regulatory approval process is expensive, time consuming and uncertain and may prevent us or any collaborators from obtaining approvals for the commercialization of some or all of our product candidates.
- If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to our business.
- If we are unable to obtain and maintain sufficient patent protection for any product candidates, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our product candidates may be adversely affected.
- Public health epidemics or outbreaks, including COVID-19, have had, and may continue to have, an adverse impact on our business.

PART I

Item 1. BUSINESS

Overview

We are a biopharmaceutical company committed to developing new standards of care for the frontline treatment of patients with hematologic malignancies. Driven by the motivation to help patients with blood disorders that have largely eluded other targeted approaches, we are advancing a late-stage clinical pipeline which includes our lead product candidates:

- Tamibarotene, a selective retinoic acid receptor alpha, or $RAR\alpha$, agonist for which we are conducting SELECT-MDS-1, a Phase 3 clinical trial evaluating tamibarotene in combination with azacitidine in a genomically defined subset of patients with higher-risk myelodysplastic syndrome, or HR-MDS, and for which we are conducting SELECT-AML-1, a randomized Phase 2 clinical trial evaluating tamibarotene in combination with venetoclax and azacitidine in a genomically defined subset of newly diagnosed patients with acute myeloid leukemia, or AML, who are not suitable candidates for standard intensive chemotherapy; and
- SY-2101, a novel oral form of arsenic trioxide, or ATO, which we are evaluating in a dose confirmation study in patients with newly diagnosed low-risk acute promyelocytic leukemia, or APL.

In addition, we are evaluating SY-5609, a highly selective and potent oral inhibitor of cyclin-dependent kinase 7, or CDK7, as a single agent in patients with select solid tumors and in combination with gemcitabine, a chemotherapy, in pancreatic cancer patients in a Phase 1 clinical trial. SY-5609 is also being evaluated in combination with atezolizumab, a PD-L1 inhibitor, in BRAF-mutant colorectal cancer in an arm of a Phase 1/1b clinical trial sponsored by F. Hoffmann-La Roche AG, or Roche, which is actively enrolling.

We also have multiple preclinical and discovery programs in oncology, including SY-12882, our oral CDK12 inhibitor, and programs targeting the inhibition of CDK11 and WRN. We are currently exploring partnership opportunities for SY-5609 and for our oncology discovery programs. We have also entered into a collaboration with Global Blood Therapeutics, Inc., now a subsidiary of Pfizer Inc., or GBT, to discover, develop and commercialize novel therapies for sickle cell disease and beta thalassemia.

Our Targeted Hematology Portfolio

We are advancing two clinical-stage drug candidates, tamibarotene and SY-2101, across three genomically defined patient populations in HR-MDS, AML and APL. Together, we believe these programs provide us the opportunity to address high unmet medical needs of patients with targeted therapies for hematologic disorders.

Tamibarotene

Overview

Tamibarotene is an oral, potent and selective agonist of the transcription factor $RAR\alpha$. At the 62nd American Society of Hematology Annual Meeting and Exposition held in December 2020, or ASH 2020, we presented data from our fully enrolled Phase 2 clinical trial assessing the safety and efficacy of tamibarotene in combination with azacitidine in 22 newly diagnosed AML patients who are “unfit,” meaning that they are not suitable candidates for standard intensive chemotherapy, who were prospectively selected using our proprietary *RARA*, the gene that codes for $RAR\alpha$, biomarker assay, as well as in 29 newly diagnosed unfit AML patients who do not overexpress *RARA*, who were enrolled to support the development of a commercial companion diagnostic test for tamibarotene. Based on these data and our assessment of ongoing areas of high unmet need, we are advancing tamibarotene in combination with azacitidine in SELECT-MDS-1, a registration-enabling Phase 3 clinical trial in newly diagnosed HR-MDS patients with *RARA* gene overexpression. We are currently dosing patients in SELECT-MDS-1, and we expect to complete enrollment in the fourth quarter of 2023 and report data from the SELECT-MDS-1 trial in the third quarter of 2024.

We are also advancing tamibarotene in combination with venetoclax and azacitidine in SELECT-AML-1, a randomized Phase 2 clinical trial of newly diagnosed unfit AML patients who are positive for *RARA* overexpression. At the 64th American Society of Hematology Annual Meeting held in December 2022, or ASH 2022, we presented data from six response-evaluable patients from the safety lead-in portion SELECT-AML-1, in which treatment with the triplet combination of tamibarotene, venetoclax and azacitidine demonstrated an 83 percent composite complete response rate and rapid onset of action, with no evidence of increased toxicity relative to historical data of the venetoclax and azacitidine doublet

combination. Based on these data, we plan to evaluate the safety and efficacy of tamibarotene in approximately 80 patients randomized 1:1, directly comparing the triplet of tamibarotene, venetoclax and azacitidine to the doublet of venetoclax and azacitidine. We initiated the randomized portion of the trial in the first quarter of 2023, and expect to report initial randomized data in the fourth quarter of 2023 and additional data in 2024.

Tamibarotene Development Plan

Based on the clinical activity and favorable safety and tolerability profile of tamibarotene in combination with azacitidine as well as an assessment of ongoing areas of high unmet need within the evolving treatment landscape, we advanced tamibarotene in combination with azacitidine in SELECT-MDS-1, a registration-enabling Phase 3 clinical trial in newly diagnosed HR-MDS patients who are positive for *RARA* overexpression. HR-MDS is a hematologic malignancy that exists on the same disease continuum as AML, with the two diseases diagnostically distinguished by the percentage blasts in the bone marrow. We believe that approximately 50% of HR-MDS patients and approximately 30% of AML patients are positive for *RARA* overexpression. In an earlier clinical trial evaluating tamibarotene as a single agent, hematologic response was observed in 60% (3/5) of evaluable patients with relapsed or refractory HR-MDS, including one patient with a marrow CR.

Informed by feedback from the U.S. Food and Drug Administration, or FDA, we are enrolling newly diagnosed HR-MDS patients who overexpress *RARA* in a double-blind placebo-controlled randomized study to receive tamibarotene in combination with azacitidine or placebo with azacitidine, respectively. In recent communications, the FDA has continued to support the use of the CR rate as an acceptable efficacy endpoint for regulatory decision-making for treatments of newly diagnosed higher-risk MDS with supporting data on durability of remission. The study will enroll approximately 190 patients randomized 2:1 into the experimental vs. control arms, respectively. The trial is designed with 90% power and a one-sided alpha of 0.025 to detect a difference in CR rates between the experimental and control arms. In January 2022, the FDA granted Fast Track Designation to tamibarotene in combination with azacitidine for the treatment of adults with newly diagnosed HR-MDS who are positive for *RARA* overexpression. We are currently dosing patients in SELECT-MDS-1, and we expect to complete enrollment in the fourth quarter of 2023 and report data from the SELECT-MDS-1 trial in the third quarter of 2024.

In addition, we advanced tamibarotene in combination with venetoclax and azacitidine in newly diagnosed unfit AML patients who are positive for *RARA* overexpression. Our ongoing Phase 2 clinical trial, known as SELECT-AML-1, included a single-arm safety lead-in to confirm the dosing regimen of the triplet to be used in the randomized portion of the trial, which will evaluate the safety and efficacy of tamibarotene in combination with venetoclax and azacitidine compared to venetoclax and azacitidine in approximately 80 patients randomized 1:1. The trial will also evaluate the triplet as a salvage strategy for patients in the control arm who do not respond to venetoclax and azacitidine in the control arm. We initiated the randomized portion of the trial in the first quarter of 2023, and expect to report initial randomized data in the fourth quarter of 2023 and additional data in 2024.

We have entered into an agreement with a third-party commercial provider to provide a validated laboratory test under Clinical Laboratory Improvement Amendment, or CLIA, guidelines using a diagnostic platform and approach that is being used to prospectively enroll patients with *RARA* gene overexpression in our clinical trials. In March 2022, we entered into a Master Collaboration Agreement and associated project work plan with Qiagen Manchester Limited, or Qiagen, pursuant to which Qiagen will develop and commercialize a companion diagnostic for this biomarker.

Tamibarotene in Combination with Azacitidine

In October 2018, we published preclinical data in *Haematologica*, a peer-reviewed journal of the European Hematology Association, supporting the rationale for combining tamibarotene with hypomethylating agents such as azacitidine in AML patients with *RARA* overexpression. These data showed that tamibarotene in combination with azacitidine resulted in synergistic anti-proliferative effects supported by evidence of DNA damage and apoptosis and, in patient-derived xenograft models of AML with *RARA* overexpression, tamibarotene in combination with azacitidine showed both greater clearance of tumor cells in bone marrow and other tissues and greater duration of response, compared to either azacitidine or tamibarotene alone.

We presented data at ASH 2020, which was later published in Blood Advances in 2022, from our fully enrolled Phase 2 clinical trial evaluating the safety and efficacy of tamibarotene in combination with azacitidine in newly diagnosed AML patients who are not suitable candidates for standard chemotherapy, as well as in R/R AML patients who overexpress *RARA*. Fifty-one newly diagnosed unfit AML patients, including those with and without *RARA* gene overexpression, were

eligible for a safety analysis. Eighteen patients who overexpress *RARA* were evaluable for clinical response. In those patients, the data showed that:

- The composite CR rate was 61% (11/18), including nine patients (50%) achieving CR and two patients (11%) achieving complete response with incomplete blood count recovery, or CRi.
 - 89% (8/9) of CRs were deep molecular or cytogenetic CRs.
 - Responses were seen across AML risk groups, including patients with mutations that are typically associated with poor outcomes.
- The median time to initial composite CR was 1.2 months.
- The median duration of composite complete remission was 10.8 months, and median overall survival, or OS, among patients who achieved a CR or CRi was 18.0 months.
- 72% (13/18) of patients achieved or maintained transfusion independence.

For the 28 patients who were negative for *RARA* overexpression and who were evaluable for clinical response, the data showed that the overall response rate, or ORR, was 43% (12/28), with a composite complete response rate of 32% (9/28), including seven patients (25%) achieving CR and two patients (7%) achieving CRi. The median time to initial composite complete remission was 3.0 months, and the median duration of composite complete remission was 10.3 months.

Tamibarotene in combination with azacitidine was generally well-tolerated with no evidence of increased toxicity relative to either as a single agent, including rates of myelosuppression that were comparable to single-agent azacitidine.

We also presented translational data demonstrating that most newly diagnosed unfit AML patients enrolled in our Phase 2 study who were positive for *RARA* overexpression had a monocytic disease phenotype that is associated with resistance to venetoclax. These data suggest that the *RARA* biomarker not only selects for patients who are more likely to respond to treatment with tamibarotene but also for patients who may be less likely to benefit from treatment with venetoclax.

Tamibarotene in Combination with Venetoclax and Azacitidine

At ASH 2022, we presented data from the safety lead-in portion of our ongoing SELECT-AML-1 Phase 2 trial evaluating tamibarotene in combination with venetoclax and azacitidine in newly diagnosed, unfit patients with AML and *RARA* gene overexpression. As of October 13, 2022, eight newly diagnosed, unfit patients who were positive for *RARA* overexpression had been enrolled in the trial, including six who were evaluable for response. The median age of the patients was 61 (ranging from 55-82) and the median percent blasts at baseline was 63% (ranging from 39-100%). In this population, tamibarotene in combination with venetoclax and azacitidine administered at approved doses showed no evidence of increased toxicity relative to the doublet combination of venetoclax and azacitidine. This includes rates of myelosuppression, which were comparable to reports with venetoclax and azacitidine in this population. Serious adverse events, or SAEs, were reported in all six patients. The most frequently occurring SAEs included febrile neutropenia (66%) and pneumonia (50%). The majority of non-hematologic AEs were low grade and reversible. The most frequently occurring non-hematologic AEs included pneumonia (66%), cough (50%), anxiety (50%), decreased appetite (50%) and rash (50%).

Among these patients, the CR/CRi rate, as defined by Revised International Working Group, or IWG, criteria was 83%, consisting of two patients (33%) who achieved a CR and three patients (50%) who achieved a CRi. Four of five patients (80%) who achieved a CR or CRi had a high monocytic expression score, or MES, which may be associated with venetoclax resistance. The median time to CR/CRi response was 33 days, ranging from 25-88 days, the median duration of treatment was 76.5 days, ranging from 20-104 days, and the median duration of follow-up was 107 days, ranging from 56-314 days. These early data compare favorably to the standard-of-care combination of venetoclax and azacitidine, which shows composite CR rates of 66% in newly diagnosed unfit AML patients.

Tamibarotene Market Opportunity

We believe that tamibarotene has the potential to address significant unmet medical need across a range of cancer populations with *RARA* gene overexpression, and, despite a significant number of new product approvals in AML since 2018, that there continues to be a significant unmet medical need in that indication.

We believe that approximately 21,000 patients are diagnosed with HR-MDS in the United States and Europe annually and we expect the total addressable market opportunity for MDS patients of all risk groups to grow to approximately \$3.3 billion by 2026. In addition, we believe that approximately 25,000 patients are diagnosed with unfit AML in the United States and Europe annually and we expect the overall total addressable market opportunity for all AML patients (fit and unfit for treatment with standard intensive chemotherapy) to grow to be approximately \$6.6 billion by 2025. Based on data from our clinical trials, we believe approximately 50% of MDS patients and approximately 30% of AML patients with *RARA* gene overexpression.

HR-MDS is progressive in nature and has a poor prognosis. Disease-related cytopenias result in significant morbidity and mortality, with more than half of HR-MDS patients progressing to AML. There have been no new drug approvals for HR-MDS since 2006 other than hypomethylating agents, or HMAs. Azacitidine is an HMA that represents the current standard of care but offers a low CR rate of 17%, with a median overall survival of approximately 18.6 months. It is estimated that more than half of newly diagnosed AML patients are elderly or unfit for treatment with intensive therapies, underscoring the need for well-tolerated therapies that can be used in combination. Venetoclax with azacitidine is the standard of care, with a 37% CR rate and median OS of 14.7 months. Approximately one-third of patients do not respond, and nearly all relapse with a very poor prognosis, with median OS of 2.4 only months. We believe that tamibarotene has the potential to provide a meaningful benefit for HR-MDS patients and newly diagnosed unfit AML patients who are positive for *RARA* overexpression.

SY-2101

Overview

In December 2020, we acquired from Orsenix, LLC, or Orsenix, a novel oral form of ATO, which we refer to as SY-2101. SY-2101 is in development for the treatment of APL, a subtype of AML defined by a fusion of the *RARA* and promyelocytic leukemia, or *PML*, genes. An intravenously administered, or IV, formulation of ATO is approved for use in combination with All-Trans-Retinoic-Acid, or ATRA, in patients with newly diagnosed lower-risk APL and, while curative in more than 80% of patients, its administration requires up to 140 two- to four-hour infusions over the typical course of induction and consolidation treatment. We believe SY-2101 has the potential to become the standard-of-care frontline therapy for APL by providing a substantially more convenient option that reduces the treatment burden on patients, improving access, and lowering costs to the healthcare system. In a prior Phase 1 clinical trial, SY-2101 demonstrated bioavailability, pharmacokinetic, or PK, exposures similar to IV ATO, and a generally well-tolerated safety profile. We are currently conducting a Phase 1 clinical trial of SY-2101 in newly diagnosed APL patients that is designed to confirm the dose for a future registration-enabling study. We plan to provide an update on the dose confirmation study, as well as the development path and timing for further evaluation of SY-2101 in a registration enabling study in APL, in the second half of 2023.

SY-2101 Clinical Data and Development Plan

SY-2101 has been evaluated in a prior Phase 1 PK study, which included three dose cohorts of 5 mg, 10 mg and 15 mg, given once daily. The study enrolled 12 patients with advanced hematologic malignancies, including six patients with R/R MDS, four patients with R/R AML, and two patients with chronic myelomonocytic leukemia. The median age of these patients was 76.5 years (with patients ranging from 45 to 81 years), and patients had a median of two prior therapies (with patients ranging from one to five prior therapies). The study showed that SY-2101 is bioavailable and achieves exposure levels in the range of the approved IV dose. It was generally well-tolerated at all doses, with the majority of adverse events being low-grade. Specifically, investigators reported preliminary responses in two MDS patients, observing one patient with marrow remission at two and five months after start of dosing, and another patient had bone marrow response and became eligible for transplant. Steady-state plasma concentration was reached on day 15. Exposure levels of SY-2101 at the 15 mg dose were comparable to the IV ATO approved dose (0.15 mg/kg) for adult patients, based on IV ATO historical data.

We are dosing patients in a dose confirmation study of SY-2101. The ongoing dose confirmation study is designed to evaluate the PK, food effect, safety and tolerability of SY-2101 and is expected to enroll between six and 24 adult APL patients undergoing consolidation with IV ATO plus ATRA. Participants receive a single dose of 15 mg of SY-2101 in both the fasted and in the fed state, and a single dose of IV ATO for PK assessments, with flexibility to allow for other SY-2101 doses to be evaluated. Daily administration of SY-2101 is also being evaluated in a multiple-dose treatment module substituting for IV ATO during consolidation to assess steady state SY-2101 PK and safety.

Based on preliminary data available to date in our ongoing Phase 1 dose confirmation study, SY-2101 administered at 15 mg achieved comparable PK (AUC and Cmax) exposures to IV ATO at the approved dose of 0.15 mg/kg. Additionally, based on the data available to date, SY-2101 showed high oral bioavailability of approximately 80% and continues to support a favorable tolerability profile. We believe this is the first cross-over data directly comparing the PK of SY-2101 to the approved IV dose ATO.

To date, feedback from the FDA and the European Medicines Agency, or EMA, in the context of the original SY-2101 PK data supports a single registration-enabling study of approximately 215 patients with newly diagnosed low-risk APL, randomized 2:1 to receive SY-2101 or IV ATO and designed with molecular complete response and event-free survival as primary endpoints for potential approval. Based on the emerging PK cross-over data directly comparing SY-2101 to the approved dose of IV ATO in our dose confirmation trial, and assuming that additional data is supportive, we believe there may be an opportunity to explore a more efficient registration pathway to potential approval.

SY-2101 Market Opportunity

APL is a subtype of AML, defined by a genetic fusion of the *RARA* and *PML* genes, and represents about 10% of AML cases. In APL, promyelocytes are overproduced and accumulate in the bone marrow and blood, resulting in signs and symptoms of the disease.

Approximately 2,000 patients are diagnosed with APL in the United States and Europe annually. We do not believe there are any oral formulations of ATO in development or on the market for the treatment of APL in the United States or Europe.

Contingent Obligations to Orsenix

In December 2020, we entered into an Asset Purchase Agreement with Orsenix, pursuant to which we acquired all of Orsenix's assets related to SY-2101. Under the terms of the Asset Purchase Agreement, we paid Orsenix an upfront fee of \$12.0 million. In addition, we are required to pay Orsenix single-digit million milestone payments related to the development of SY-2101 in indications other than APL, \$6.0 million following the achievement of a regulatory milestone related to the development of SY-2101 in APL, and up to \$10.0 million upon the achievement of certain commercial milestones with respect to SY-2101. Our obligation to pay the commercial milestone payments expires following the tenth anniversary of the first commercial sale of SY-2101. The Asset Purchase Agreement requires us to use commercially reasonable efforts to develop and commercialize SY-2101 for APL in the United States during such period, and to use commercially reasonable efforts to dose the first patient in a Phase 3 clinical trial of SY-2101 on or before the third anniversary of the closing of the transaction; however, we retain sole discretion to operate the acquired assets as we determine.

Earlier-Stage Programs

We are currently evaluating SY-5609, our highly selective and potent oral CDK7 inhibitor, in a Phase 1 clinical trial as a single agent in R/R patients with select solid tumors, and in combination with gemcitabine and with gemcitabine plus nab-paclitaxel in patients with metastatic pancreatic cancer. In addition, Roche continues to enroll patients in the arm of its ongoing Phase 1/1b INTRINSIC trial evaluating SY-5609 in combination with atezolizumab, its PD-L1 inhibitor, in BRAF-mutant colorectal cancer patients.

We also have multiple preclinical and discovery programs in oncology, including SY-12882, our oral CDK12 inhibitor, and programs targeting the inhibition of CDK11 and WRN. We are currently exploring partnership opportunities for SY-5609 and for our discovery-stage oncology programs.

Overview

SY-5609 is a highly potent and selective small molecule CDK7 inhibitor that can be administered orally. CDK7, a member of the CDK family, is a transcriptional kinase that plays a central role in two processes that cancer cells use to survive and thrive: increased expression of cancer-promoting genes, and uncontrolled cell cycle progression. CDK7 activity has been implicated in a range of solid tumors and blood cancers. We believe that inhibiting CDK7 preferentially lowers the expression of disease-driving transcription factors and anti-apoptotic proteins, resulting in the preferential killing of cancer cells over non-cancerous cells. We also believe that selective inhibition of CDK7 interferes with cancer-driving adaptations at multiple points in the cell cycle, promoting the induction of apoptosis, or cell death.

Phase 1 Dose Escalation Study of SY-5609 in Patients with Pancreatic Cancer and Select Solid Tumors

At the European Society for Medical Oncology Congress held in September 2021, or ESMO 2021, we presented data from the dose-escalation portion of the Phase 1 multi-center, open-label study of SY-5609 evaluating patients with advanced breast, colorectal, lung, ovarian and pancreatic cancers, as well as patients with solid tumors of any histology harboring Rb pathway alterations.

Patients were treated in cohorts exploring continuous daily dosing as well as intermittent dosing regimens, including seven days on treatment and seven days off, or 7d on/7d off, and five days on treatment and two days off, or 5d on/2d off, schedules. As of a July 6, 2021 data cut-off, 54 patients treated with single-agent SY-5609 in the study were eligible for a safety analysis and 45 patients were evaluable for clinical response. The median age of patients enrolled in the study was 65.5. Patients had been heavily pre-treated with as many as eight prior therapies and a median of four prior therapies.

Across all doses and schedules, the majority of adverse events, or AEs, were low-grade and reversible, and there was a low rate of discontinuations due to AEs. The most common treatment-emergent AEs were gastrointestinal (nausea, diarrhea, decreased appetite, abdominal pain, vomiting), fatigue, thrombocytopenia, and anemia. Tolerability was optimized with the 7d on/7d off schedule, which had the lowest rates of treatment-emergent AEs relative to other regimens, while demonstrating comparable rates of stable disease, or SD, as seen with more dose-intense regimens, supporting the selection of this schedule for further development of SY-5609. The maximum tolerated dose of the 7d on/7d off schedule has not yet been reached as of the data cut-off date. Changes in POLR2A mRNA expression, a pharmacodynamic marker for CDK7 inhibition were associated with anti-tumor activity and were sustained for at least three days following drug cessation, supporting intermittent dosing. As of the data cut-off date:

- Thirteen response-evaluable patients (29%) had achieved SD, with tumor regressions of up to 20% in six of those patients, across multiple tumor types.
- The most substantial clinical activity was observed in heavily pre-treated patients with advanced pancreatic cancer.
 - Five of 13 (39%) evaluable patients achieved SD, with tumor reductions in two of those SD patients.
 - Reductions in the CA 19-9 tumor marker, which is used in clinical practice to monitor tumor progression, were observed in three of four pancreatic cancer patients with serial CA 19-9 data, with these reductions ranging from 32% to 72%.
 - Notably, one metastatic pancreatic cancer patient who had failed two prior lines of therapy and relapsed after a third line of treatment experienced prolonged SD of up to ten months.
- The analysis of clinical activity by tumor type and mutational status supported the mechanistic rationale for SY-5609 in Rb-altered and KRAS-mutant cancers.

Based on these data, we are evaluating an expansion cohort that includes two arms evaluating SY-5609 in combination with chemotherapy for the treatment of pancreatic cancer, one of which is evaluating SY-5609 in combination with gemcitabine in patients in first or second relapse who have progressed following treatment with the chemotherapy regimen known as FOLFIRINOX, and the other is exploring a SY-5609 in combination with gemcitabine and nab-paclitaxel

in patients following first relapse after FOLFIRINOX. SY-5609 is administered 7d on/7d off at a starting dose of 4 mg in both the gemcitabine combination and triplet combination arms, and the combination agents are administered at the approved doses. The study is designed to evaluate safety and tolerability, as well as efficacy measures such as progression free survival and disease control rate, or DCR, which is the combined rate of CR, partial response, or PR, and SD.

As of a October 12, 2022 safety data cut-off, a maximum tolerated dose, or MTD, of single agent SY-5609 administered in a 7 day on/7 day off dosing regimen has not been reached. The 10 mg dose level did not result in any dose limiting toxicities, or DLTs, further supporting the tolerability of the 7 day on/7 day off dosing regimen in which 30 patients have been dosed across five dose levels (4, 5, 6, 7, and 10 mg), with one DLT observed at the 4 mg single agent dose level. PK analyses demonstrated an expected increase in SY-5609 exposure levels, with the 10 mg single-agent dose also supporting a preliminary exposure-response relationship. At the time of the October 20, 2022 clinical activity data cut off, two of three study patients treated at the 10 mg single-agent dose level were response evaluable, with two of two response-evaluable patients achieving SD (one with pancreatic ductal adenocarcinoma, or PDAC, and one with colorectal cancer, or CRC), with the PDAC patient experiencing a 10% tumor reduction. As of the safety data cut-off, an MTD for either the doublet or the triplet has not been reached in the 7 day on/7 day off dosing regimen, with dosing of SY-5609 up to 5 mg in the doublet and up to 4 mg in the triplet regimen, respectively. SY-5609 has been combined with gemcitabine and with gemcitabine plus nab-paclitaxel, with no new safety signals identified and the majority of AEs being low grade and reversible. The most common related AEs in the cohort with SY-5609 and gemcitabine, where the highest SY-5609 doses were evaluated in combination with chemotherapy, included fatigue, nausea, decreased appetite and decreased platelet count (all low grade), with one patient experiencing a DLT of grade 3 diarrhea at the 5 mg SY-5609 dose level. No DLTs were reported in patients treated with SY-5609 in combination with gemcitabine/nab-paclitaxel. As of the clinical activity data cut-off, initial doublet activity of SY-5609 plus gemcitabine in PDAC included a confirmed PR by Response Evaluation Criteria in Solid Tumors, or RECIST, accompanied by a 98% reduction in the CA 19-9 tumor marker from a baseline of 60,357 U/mL to 968 U/mL, in one of four response evaluable patients treated at the 4 mg SY-5609 dose level, corresponding to a 25% DCR, and SD in three of four response evaluable patients treated at the 5 mg SY-5609 dose level, corresponding to a 75% DCR, for an overall DCR of 50% (four out of eight) in response evaluable patients. There is preliminary evidence for an exposure-response relationship, with the responding patient who achieved a confirmed PR demonstrating higher-than-average exposure relative to other patients at that dose. Two of three patients treated at the 4 mg dose level in the triplet regimen cohort were response evaluable, including one with SD. We have completed enrollment in the single agent cohort for select solid tumors and in the doublet combination cohort in PDAC patients, and we are currently seeking a partnership for the further development of SY-5609.

BRAF-Mutant Colorectal Cancer

BRAF mutations, present in 10% of colorectal cancer patients, are powerful activators of cell signaling and transcriptional programs. At the 2020 American Society of Clinical Oncology Virtual Scientific Program, or ASCO 2020, we reported the results of a series of preclinical studies of SY-5609 in colorectal cancer cell lines, as well as in 30 independent patient-derived xenograft, or PDX, models of colorectal cancer, including BRAF-mutant, KRAS-mutant and wild-type models. The data showed that SY-5609:

- Potently inhibited proliferation and induced G2/M cell cycle arrest in KRAS- and BRAF-mutant colorectal cancer cell lines in vitro.
- Induced dose-dependent tumor growth inhibition, including complete regressions that were sustained after treatment discontinuation, with repeated daily dosing at well-tolerated doses that were associated with dose-dependent expression changes in cell cycle markers E2F1 and CCNB1 and the transcriptional marker POLR2A in a BRAF-mutant PDX model.
- Resulted in at least 50% tumor growth inhibition in 67% (20/30) of PDX models, and at least 90% tumor growth inhibition in 23% (7/30) of PDX models, including in models derived from heavily pre-treated patients, at well-tolerated doses.
 - Deeper responses, defined as at least 90% tumor growth inhibition, were observed more frequently in models with BRAF mutations (50%, or 5/10) relative to KRAS-mutant or wild-type models (10%, or 1/10 each).

oRegressions were seen in two BRAF-mutant models and one KRAS-mutant model.

Preclinical studies have also demonstrated that CDK7 inhibition enhances anti-tumor activity of PD1 inhibition, inducing DNA replication stress and genome instability in cancer cells and triggering immune-response signaling. In animal models, CDK7 inhibitors have been shown to enhance tumor response to anti-PD1 immunotherapy, prolonging overall survival and increasing immune cell infiltrates.

We believe that these preclinical data support the exploration of SY-5609 in BRAF-mutant colorectal cancer in combination with a PDL1 inhibitor as part of Roche's Phase 1/1b INTRINSIC trial. In August 2021, we announced entry into a clinical supply agreement with Roche, pursuant to which we agreed to supply SY-5609 for a combination dosing cohort with atezolizumab in Roche's ongoing Phase 1/1b INTRINSIC trial, which is evaluating multiple targeted therapies or immunotherapy, including atezolizumab, as single agents or in rational specified combinations in molecularly defined subsets of colorectal cancer patients. SY-5609 is being evaluated in combination with atezolizumab in patients with BRAF-mutant disease, and this arm of the trial is now actively enrolling. Under the terms of the agreement, Roche will sponsor and conduct the Phase 1/1b study to evaluate the safety, tolerability and preliminary efficacy of the combination of SY-5609 and atezolizumab and will assume all costs associated with the study. In exchange for providing SY-5609, we will receive access to the data on SY-5609 in combination with atezolizumab. We retain all rights to SY-5609.

Discovery-Stage Oncology Programs

We currently have several oncology programs in our preclinical and discovery pipeline targeting the inhibition of CDK12, CDK11, and WRN. We are currently exploring partnership opportunities for these programs.

Our CDK12 inhibitor program builds on our capabilities to discover potent and selective small molecule inhibitors to specific members of the CDK family. In preclinical studies, we have observed that inhibiting CDK7 results in different transcriptional effects than inhibiting CDK12, pointing to distinct therapeutic opportunities to benefit patients with difficult-to-treat cancers. Specifically, we believe that a selective CDK12 inhibitor presents a therapeutic opportunity in cancers that have a dependency on DNA repair. In July 2022, we nominated SY-12882, our oral, potent, and selective CDK12 inhibitor, as a drug candidate for which investigational new drug, or IND, -enabling studies could be conducted. Preclinical data presented at the American Association for Cancer Research (AACR) annual meeting in April 2022 demonstrated that selective CDK12 inhibition resulted in strong anti-tumor activity as a single agent and in combination with a DNA damaging agent and in combination with a poly adenosine diphosphate-ribose polymerase, or PARP, inhibitor in models of breast, lung, and ovarian cancer.

Sickle Cell Disease and Beta Thalassemia

Our objective is to provide a functional cure for sickle cell disease patients by switching on the gamma-globin gene with an oral medicine. We have focused our efforts to date on LRF (leukemia/lymphoma-related factor) and the NuRD (nucleosome remodeling and histone deacetylation) complex as potential targets to switch on the gamma-globin gene, which is normally silenced a few months after birth. By turning on gamma-globin expression, we aim to induce the production of fetal hemoglobin, which is known to exert protective effects on the red blood cells of patients with sickle cell disease and beta thalassemia and to mitigate the clinical manifestations of those diseases.

In December 2019, we entered into a collaboration with GBT, now a subsidiary of Pfizer Inc., to discover, develop and commercialize novel therapies for sickle cell disease and beta thalassemia. See “—License and Collaboration Agreements—Global Blood Therapeutics” below.

Intellectual Property

We file patent applications directed to various compositions of matter, formulations and methods related to our product candidates and compounds in earlier stages of development and other commercially relevant inventions. As of December 31, 2022, we own 23 issued U.S. patents and 14 pending U.S. utility patent applications, excluding patents owned by Tyme Inc., our wholly owned subsidiary. We are pursuing or maintaining 121 corresponding patent applications that are pending or granted in various jurisdictions outside the United States, including Europe, Japan, Australia, Canada and China, and we own four applications that are pending in accordance with the Patent Cooperation Treaty, or PCT. A significant

portion of the patents and applications we own pertain to our product candidates that are in clinical or pre-clinical development, to methods of using them in the treatment of disease, and to methods of selecting patients for treatment based on biomarker expression.

Our intellectual property portfolio as of December 31, 2022 is further described below. For some of our pending patent applications, prosecution has yet to commence. Prosecuting patent applications to allowance is often a lengthy process, during which the scope of the claims initially submitted for examination by various patent offices is often significantly narrowed, and some claims may never be granted. It is possible that we will amend the claims of our pending patent applications to limit their scope. We may also elect to abandon some of our pending patent applications, particularly those pending outside of the United States, if we determine these applications do not have strategic significance to our programs or platform.

Tamibarotene

The patent portfolio we own for tamibarotene contains seven issued U.S. patents, two pending U.S. utility patent applications, 32 applications pending or granted in countries other than the United States, including Europe, Japan, Australia, Canada, China, Russia, Israel and Mexico, and two pending PCT applications. Generally, these patents and applications disclose methods of identifying and treating patients who are sensitive to *RARA* agonists, including tamibarotene, based on the expression of certain biomarkers, including *RARA*. The applications disclose methods of treating selected patients with tamibarotene alone or with a combination of tamibarotene and a second agent, such as azacitidine. One of our issued patents, U.S. Patent No. 9,845,508, covers methods of diagnosing and treating human patients suffering from non-APL AML by administering tamibarotene; the patients are diagnosed based on the level of *RARA* messenger RNA, or mRNA, previously determined to be present in a sample of diseased cells from the subject. The granted claims of a second patent, U.S. Patent No. 10,167,518, cover methods of treating human subjects suffering from MDS. Selection of subjects for treatment is again based on the level of *RARA* mRNA expression, and subjects with *RARA* overexpression are treated with tamibarotene. A third patent, U.S. Patent No. 9,868,994, covers methods of treating non-APL AML or MDS by administering tamibarotene to a patient when a defined sample obtained from the patient is determined to have an elevated level of *IRF8* mRNA or elevated levels of both *IRF8* and *RARA* mRNA. A fourth patent, U.S. Patent No. 10,240,210, covers methods of treating non-APL AML or MDS with a combination of tamibarotene and azacitidine when a defined sample from the subject has been determined to have an elevated *RARA* mRNA level or an elevated *IRF8* mRNA level. A fifth patent, U.S. Patent No. 10,697,025, covers methods of treating subjects who have non-APL AML with tamibarotene; treatment proceeds when a sample of diseased cells from the subject was determined to have a super enhancer associated with a *RARA* gene or a level of primary RNA transcripts from the *RARA* gene that is equal to or above a pre-determined threshold. A sixth patent, U.S. Patent No. 11,053,552, covers methods of treating non-APL AML or MDS by administering a combination of tamibarotene and a second therapeutic agent, with further specification of the analysis of an *IRF8* biomarker and/or a *RARA* biomarker. A seventh patent, U.S. Patent No. 11,447,831, covers methods of treating subjects who have MDS with tamibarotene; treatment proceeds when a sample of diseased cells from the subject is determined to have a super enhancer associated with a *RARA* gene or a level of primary RNA transcripts from the *RARA* gene that is equal to or above a pre-determined threshold. We believe these seven U.S. patents are eligible for listing in the FDA's "Orange Book." These patents, as well as any additional patents that may grant from applications claiming the benefit of the same filing date as the currently granted patents, have statutory expiration dates no earlier than March 2036. Patent term extensions could result in later expiration dates.

In addition, we have an exclusive license from TMRC to practice the inventions claimed in one U.S. patent and five patents or applications granted or pending in the United States or other jurisdictions, including Canada and Europe. The claims of the U.S. patent are directed to a tamibarotene capsule preparation. We do not have composition of matter patent protection with respect to tamibarotene.

SY-2101

The patent portfolio we own for SY-2101 contains six issued patents, three of which were obtained in the U.S., one of which was granted in Europe, one of which was granted in Mexico, and one of which was granted in Japan. In addition, applications remain pending in the U.S. and other jurisdictions, including Europe, Japan, Australia, Canada and China. Generally, these patents and applications disclose methods of making lyophilized compositions comprising arsenic and formulations containing the lyophilized arsenic that can be orally administered to patients having acute promyelocytic leukemia and other hematological malignancies. One of our issued patents, U.S. Patent No. 10,111,836, covers methods of preparing an oral pharmaceutical formulation comprising a lyophilized composition comprising arsenic or lyophilized arsenic

trioxide. A second patent, U.S. Patent No. 10,272,045, covers distinct methods of preparing a lyophilized composition comprising arsenic. A third patent, U.S. Patent No. 10,653,628, covers a solution for use in the lyophilization of a pharmaceutical compound comprising arsenic trioxide. These patents, as well as any additional patents that may grant from applications claiming the benefit of the same filing date as the currently granted patents, have statutory expiration dates no earlier than February 2036. Patent term extensions could result in later expiration dates.

SY-5609 and Other CDK7 Inhibitors

The patent portfolio we own for SY-5609 and our other CDK7 inhibitors, including SY-1365, contains patents and patent applications generally directed to the inhibitors, pharmaceutical formulations containing them, and methods of making and using them, including their use in treating various biomarker-selected patient populations. As of December 31, 2022, we own nine issued U.S. patents, eight pending U.S. patent applications, 70 corresponding applications pending or granted in countries outside the United States, including Europe, Japan, Australia, Canada and China and two pending applications filed in accordance with the PCT. Any patent that has issued or will issue and that claims the benefit of the priority date of one or more of these patents or patent applications will have a statutory expiration date ranging from October 2034 to November 2042. Patent term adjustments or patent term extensions could result in later expiration dates.

Of the nine issued U.S. patents we own: (1) U.S. Patent No. 10,106,526 covers compounds and pharmaceutical compositions generically describing SY-1365; (2) U.S. Patent No. 10,059,690 specifically claims SY-1365 and pharmaceutical compositions containing SY-1365; (3) U.S. Patent No. 10,519,135 covers pharmaceutical compositions containing stereoisomers of SY-1365; (4) U.S. Patent No. 10,336,760 covers CDK7 inhibitors conforming to the structural formula provided; (5) U.S. Patent No. 10,308,648 covers CDK7 inhibitors conforming to the structural formula provided as well as pharmaceutically acceptable salts, solvates, hydrates, tautomers, and stereoisomers thereof; (6) U.S. Patent No. 10,865,206 covers pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a CDK7 inhibitor conforming to the structural formula provided or a pharmaceutically acceptable salt, isotopically labeled derivative, or stereoisomer thereof; (7) U.S. Patent No. 11,083,728 covers pharmaceutical formulations containing SY-1365 or a pharmaceutically acceptable salt thereof; (8) U.S. Patent No. 10,738,067 covers SY-5609 and pharmaceutical compositions comprising a therapeutically effective amount thereof; and (9) US Patent No. 11,311,542 covers CDK7 inhibitors conforming to the structural formula provided and pharmaceutically acceptable salts, stereoisomers, and isotopic forms thereof. The first six of these patents have statutory expiration dates in 2035, not including available patent term extensions. The seventh patent has a statutory expiration date in 2038, not including any available patent term extension. The eighth patent has a statutory expiration date in November 2039, not including available patent term adjustments or patent term extensions. The ninth patent, covering CDK7 inhibitors, has a statutory expiration date in July of 2040, not including any available patent term extensions.

Sickle Cell Disease

As of December 31, 2022, we own one patent application that is directed to methods of treating hemoglobinopathies such as sickle cell disease, and which is pending in Australia, Canada, Europe and the United States.

Other Programs

The intellectual property portfolio we own that relates to programs other than those described above contains patents and patent applications directed to compositions of matter for inhibiting transcription factors and immuno-oncology targets in multiple compound families, and methods of treating various diseases, including cancer and immunological diseases, through inhibition of specific transcription factor(s) or gene products. As of December 31, 2022, we own four U.S. patents and three U.S. patent applications. Our issued patents numbered 10,787,444, 11,124,527 and 11,274,103 cover compounds conforming to the structures provided as well as pharmaceutically acceptable salts thereof, which are intended for use as inhibitors of Myc. These patents have statutory expiration dates in June 2036 (U.S. Patent Nos. 10,787,444 and 11,124,527) and in October 2037 (inclusive of patent term adjustment). Our issued patent, U.S. Patent No. 11,040,981, covers compounds conforming to the structures provided as well as pharmaceutically acceptable salts thereof that are intended for use as inhibitors of TAM kinases. This patent has a statutory expiration date in October 2038.

In most countries, including the United States, a patent expires 20 years from its earliest effective filing date. In the United States, a patent's term may be lengthened to compensate for delays by the U.S. Patent and Trademark Office, or USPTO, in examining and granting a patent or may be shortened if a patent is terminally disclaimed over an earlier filed

patent. A patent that covers a therapeutic agent may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. See “—Government Regulation and Product Approvals—Marketing Authorization” below for additional information on such exclusivity. If and when our products receive approval by the FDA or regulatory agencies in other countries, we expect to apply for a patent term extension on an issued patent covering a given product, depending upon the length of the clinical trials for each product and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the terms of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to exclude others from making, using, or selling our product candidates and other inventions will depend on our success in obtaining valid patent claims and enforcing those claims. One or more of our pending patent applications, and any that we may file or license from third parties in the future may not, however, proceed to grant as an issued patent. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any patent may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings in the USPTO to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us, which is highly unpredictable. In addition, because of the extensive time required for clinical development and regulatory review of a product candidate we may develop, it is possible that, before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby limiting protection such patent would afford the respective product and any competitive advantage such patent may provide.

In addition to patents and pending patent applications, we rely upon unpatentable know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, by executing non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees, collaborators, scientific advisors and consultants as appropriate. The confidentiality agreements we enter into are designed to protect our proprietary information and the agreements or clauses requiring assignment of inventions to us are designed to grant us ownership of technologies that are developed through our relationship with the respective counterparty. We cannot guarantee, however, that these agreements will afford us adequate protection of our intellectual property and proprietary information rights.

License and Collaboration Agreements

We are a party to collaborations in which we aim to use our platform to benefit patients with diseases beyond our current areas of focus, or that we believe will contribute to our ability to advance development and ultimately commercialize our product candidates. We expect to enter into additional collaborations in the future. For instance, we intend to seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. Our existing collaborations impose, and any collaborations we may enter into in the future are likely to impose, certain performance obligations on us.

In addition, we are a party to a number of license agreements under which we license patents, patent applications and other intellectual property from third parties. We enter into these agreements to augment our proprietary intellectual property portfolio. This licensed intellectual property covers some of the compounds that we are researching and developing and some of the scientific processes that we use. These licenses impose various diligence and financial payment obligations on us. We expect to continue to enter into these types of license agreements in the future.

Global Blood Therapeutics

In December 2019, we entered into a license and collaboration agreement with GBT with respect to a research collaboration to discover novel targets that induce fetal hemoglobin, in order to develop new small molecule treatments for sickle cell disease and beta thalassemia. Under the terms of the collaboration agreement, parties will use commercially reasonable efforts to identify at least one compound for the commencement of studies that are reasonably required to meet the requirements for filing an IND. Each party will be solely responsible for its own costs incurred to conduct its activities under the research plan, except that GBT will reimburse us for full-time employee and out-of-pocket costs and expenses that we incur in accordance with the agreed upon research budget. The term of the research program may be extended by one or two one-year extensions as mutually agreed upon. The parties have agreed to extend the research term for an additional year, with the term now scheduled to end in December 2023.

Under the terms of the collaboration agreement, we granted to GBT an option to obtain an exclusive, worldwide license, with the right to sublicense, under relevant intellectual property rights and know-how of our company arising from the collaboration to develop, manufacture and commercialize any compounds or products resulting from the collaboration. GBT may exercise this option at any time during the period (i) commencing on the earlier of (a) the date of GBT's designation of the first IND candidate, or (b) if no IND candidate is so designated as of the expiration of the research term, the date of expiration of the research term, and (ii) ending on the 180th day after the date of expiration or earlier termination of the research term. GBT's exercise of the option will be subject to any required filings with the applicable antitrust authority as required by the antitrust laws and satisfaction of any applicable antitrust conditions.

After any exercise of the option, GBT will be solely responsible, at its own expense, for all development, manufacturing, regulatory activities and commercialization of licensed compounds and products worldwide. Under the collaboration agreement, GBT is required to use commercially reasonable efforts to develop (including to seek and obtain regulatory approval of) and, if regulatory approval is obtained, commercialize at least one product in any and all uses in the United States and any of the United Kingdom, Germany, France, Italy and Switzerland. In addition, we have an option to co-promote the first product in the United States.

GBT made an upfront payment of \$20.0 million to us in January 2020. Should GBT exercise its license option, we could receive up to \$315 million in option exercise, development, regulatory, commercialization and sales-based milestones per product candidate and product resulting from the collaboration. We are also entitled to receive, subject to certain reductions, tiered mid-to-high single digit royalties as percentages of calendar year net sales on any licensed product. GBT's obligation to pay royalties, on a licensed product-by-licensed product and country-by-country basis, will commence on the date of the first commercial sale of such licensed product in such country and end on the later of (a) the tenth anniversary of the first commercial sale of such licensed product in such country, (b) the expiration of the last to expire valid claim in our patent rights, the jointly-owned patent rights or certain other specified patent rights that cover such licensed product in such country, and (c) the expiration of regulatory exclusivity for such licensed product in such country.

Either party may terminate the collaboration agreement for the other party's uncured material breach or insolvency, and in certain other specified circumstances, subject to specified notice and cure periods. GBT may unilaterally terminate the collaboration agreement in its entirety, for any or no reason, upon nine-months' prior written notice to us if such notice is delivered during the research term, or 90 days' prior written notice to us if such notice is delivered after the expiration or termination of the research term. Upon the termination of the collaboration agreement in certain specified cases (including any unilateral termination by GBT), GBT has agreed to grant us, effective as of the effective date of such termination, a worldwide, exclusive, royalty-bearing license, with the right to grant sublicenses, under specified intellectual property necessary or useful for the development, manufacture or commercialization of licensed compounds and products for any and all uses, as well as engage in other customary technology transfer activities.

Incyte Corporation

In January 2018, we entered into a target discovery, research collaboration and option agreement with Incyte, pursuant to which we agreed to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte has received options to obtain exclusive worldwide rights to intellectual property resulting from the collaboration for the development and commercialization of therapeutic products directed to up to seven validated targets. For each option exercised by Incyte, Incyte will have the exclusive worldwide right to use the licensed intellectual property to develop and commercialize therapeutic products that modulate the target as to which the option was exercised.

Under the terms of the collaboration agreement, Incyte paid us \$10.0 million in up-front consideration, consisting of \$2.5 million in cash and \$7.5 million in pre-paid research funding, or the pre-paid research amount. Incyte was responsible for funding our activities under an agreed-upon research plan, including amounts in excess of the pre-paid research amount. Under the collaboration agreement, we are required to use commercially reasonable efforts to conduct the research services over a period commencing on the effective date of the collaboration agreement and ending upon the completion of specified target validation activities. As of December 31, 2022, we completed all of the target validation activities allocated to us under the research plan.

We are eligible to receive target selection milestone payments and option exercise fees of up to an aggregate of \$54.0 million if Incyte selects the maximum number of targets for validation and exercises its options to obtain exclusive rights to collaboration intellectual property for therapeutic products directed to all seven validated targets. Should any therapeutic product be developed by Incyte against a target as to which Incyte has exercised its option to obtain exclusive rights to collaboration intellectual property, we will be eligible to receive milestone payments and, if approved and commercialized, royalty payments from Incyte. For each of the seven validated targets, we would become eligible to receive from Incyte a total of up to \$50.0 million in development and regulatory milestone payments. If products arising from the collaboration are approved, we would become eligible to receive from Incyte, for each validated target, a total of up to \$65.0

million in commercial milestone payments. Upon approval and commercialization of any therapeutic product resulting from the collaboration, we would become eligible to receive low single-digit royalties on net sales of such product.

The term of the collaboration agreement with Incyte will, unless terminated by a party early, expire when all royalty obligations for products arising from the collaboration expire. The agreement may be terminated by Incyte for convenience on sixty (60) days' prior written notice to us, or by us on thirty (30) days' written notice in the event Incyte or one of its affiliates or sublicensees challenges the validity or enforceability of certain patent rights controlled by us. The agreement may also be terminated by either of the parties on thirty (30) days' prior written notice in the event of an uncured material breach of the agreement by the other party or immediately in the case of certain bankruptcy events. If the collaboration agreement is terminated by Incyte for material breach, then we must refund any unexpended pre-paid research amount. Incyte's right to terminate for convenience and each party's right to terminate for uncured material breach may be exercised either with respect to the agreement in its entirety or, as applicable, in relation to the relevant validated target and associated therapeutic products.

In connection with the collaboration agreement, we sold 79,302 shares of our common stock to Incyte for an aggregate purchase price of \$10.0 million in cash, or \$126.10 per share, in a private placement. In addition, we granted to Incyte the right to purchase up to its pro rata share of the securities offered in certain subsequent offerings of our common stock or common stock equivalents, subject to the terms and conditions set forth in the stock purchase agreement. In February 2018, we sold 14,450 additional shares of our common stock to Incyte at a price of \$95.50 per share, resulting in proceeds to us of \$1.4 million. Incyte's pro rata participation rights have since expired.

TMRC

In September 2015 we entered into, and in April 2016 we amended and restated, a license agreement with TMRC, which we refer to as the TMRC license agreement, pursuant to which TMRC granted us an exclusive license, with the right to sublicense, under TMRC patent rights, data, regulatory filings and other intellectual property for the North American and European development and commercialization of tamibarotene products for the treatment of human cancer indications. In January 2021, we further amended the TMRC license agreement to expand the territory under which we are licensed to include Central and South America, Australia, Israel, and Russia. Under the TMRC license agreement, we have agreed to pay TMRC single-digit royalties based on net sales if TMRC's patents cover our product and low single-digit royalties based on net sales with respect to know-how licensed by TMRC during a predefined royalty term, and to make payments to TMRC upon meeting specified clinical and regulatory milestones in an aggregate amount of approximately \$13.0 million per indication, of which \$1.0 million was paid in the third quarter of 2016 upon successful dosing of the first patient in our Phase 2 clinical trial of tamibarotene. Under the TMRC license agreement, we must use commercially reasonable efforts to, among other things, commence development activities within one year, to develop tamibarotene in at least one cancer indication, and, following marketing approval, to market the product. The license agreement expires on the expiration of the subject patent rights or 15 years after the date of first commercial sale of product, whichever is later. The TMRC license agreement may be terminated by either party if the other party is in breach and the breach is not cured within a required amount of time or if the other party is in bankruptcy. If we have reason to do so, we may also terminate the agreement after one year from the original effective date at our sole discretion.

In connection with the TMRC license agreement, in April 2016 we entered into a supply management agreement with TMRC. Pursuant to the supply management agreement, we and TMRC have agreed to establish a joint manufacturing committee to discuss strategy for supply of tamibarotene. In addition, we have agreed to pay TMRC a fee for each kilogram of tamibarotene we procure for clinical trial or commercial use. The supply management agreement terminates on the expiration or termination of the TMRC license agreement, and our obligation to pay these fees survives the termination of the supply management agreement. In April 2016, we also entered into a standby license with TMRC and Toko Pharmaceuticals Ind. Co. Ltd., or Toko, the owner of the patent rights licensed to TMRC from which our license agreement with TMRC derives its rights, pursuant to which we obtain a standby license from Toko if Toko's license with TMRC is terminated.

We have developed our own patent portfolio related to tamibarotene, which generally discloses methods of identifying and treating patients who are sensitive to *RARα* agonists, including tamibarotene, based on the expression of certain biomarkers, including *RARA*. In January 2021, we entered into a license agreement with TMRC, which we refer to as the biomarker license agreement, under which we granted TMRC an exclusive license, with the right to grant sublicenses, under these patent rights and certain know-how that it controls related to the *RARA* biomarker for the development and commercialization of tamibarotene for human cancer indications in Japan, China, South Korea, India and Taiwan. Under the biomarker license agreement, TMRC will be obligated to pay us a low single-digit royalty on net sales of tamibarotene in these territories during a pre-specified royalty term to the extent the manufacture, use or sale of tamibarotene infringes a valid claim of the patent rights or is developed using know-how licensed to TMRC under the biomarker license agreement.

In March 2022, we entered into a master collaboration agreement and a project schedule with Qiagen. Pursuant to this agreement, Qiagen has agreed to develop and commercialize an assay as a companion diagnostic test to determine the *RARA* gene expression levels for use with tamibarotene in newly diagnosed higher-risk MDS patients.

Under the agreement, Qiagen is responsible for developing, and obtaining and maintaining regulatory approvals for the companion diagnostic test in the United States and, at our request and subject to the negotiation of mutually agreed payments, in the following additional markets: Canada, the United Kingdom, the member states of the European Economic Area, Switzerland, Mexico, Australia, Russia, Israel and Brazil. In addition, Qiagen has agreed to use commercially reasonable efforts to manufacture the companion diagnostic test and, upon negotiation of mutually agreed terms, to make the companion diagnostic test commercially available in the United States, the additional markets described above, and such other countries as the parties may mutually agree. Qiagen has agreed to undertake specified actions to minimize the risk of an inability of supply occurring for the manufacture of the companion diagnostic test.

Subject to the terms of the agreement and upon achievement of specified technical and development milestones, we are obligated to pay Qiagen up to a high single-digit million dollar payment in the agreement over the term of the initial project schedule in connection with developing and obtaining and maintaining regulatory approval for the companion diagnostic in the United States. In addition, we must reimburse Qiagen for certain pass-through costs. These amounts are subject to adjustment if the parties determine that changes in the scope of the development program are required. In addition, Qiagen will retain all proceeds from the commercialization of the companion diagnostic test. We have no financial obligations to Qiagen under the agreement on the commercialization of tamibarotene.

The initial term of the agreement expires on the later to occur of (i) the fifth anniversary of the agreement and (ii) the expiration or termination of all project schedules executed under the agreement. Thereafter, the agreement automatically renews for additional periods of one year. We may terminate the agreement or a project schedule executed under the agreement for convenience upon 90 day's prior written notice to Qiagen. Either party may terminate the agreement or any project schedule executed under the agreement, as applicable, upon a material breach of the other party that is not cured within 30 days after written notice of such breach, immediately upon the bankruptcy or insolvency of the other party, or in certain other circumstances described in the agreement. In the event that we terminate the agreement for reasons other than Qiagen's material breach or bankruptcy, we will be obligated to pay Qiagen wind-down and other costs and other final payments.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, development experience, and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that develop therapy for the treatment of cancer, including divisions of large pharmaceutical companies and biotechnology companies of various sizes.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy and targeted drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates may compete with many existing drug and other therapies, they may also be used in combination with or as an adjunct to these therapies. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors. In general, although there has been considerable progress over the past few decades in the treatment of cancer and the currently marketed therapies provide benefits to many patients, these therapies all are limited to some extent in their efficacy and frequency of adverse events. As a result, the level of morbidity and mortality from cancer remains high.

In addition to currently marketed therapies, there are also a number of medicines in late-stage clinical development to treat cancer. These medicines in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain market approval.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved medicines than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of and ease of access to companion diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize medicines that are safer, more effective, have fewer or less severe side effects, are more convenient, have greater ease of access, or are less expensive than any medicines that we may develop. Our competitors also may obtain FDA or other regulatory approval for their medicines more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic medicines. There are many generic medicines currently on the market for the indications that we are pursuing, and additional medicines are expected to become available on a generic basis over the coming years. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over competitive generic medicines.

If the product candidates of our priority programs are approved for the indications for which we are currently planning clinical trials, they will compete with the drugs discussed below and will likely compete with other drugs currently in development.

Tamibarotene

We are developing tamibarotene, our RAR α agonist, for patients with AML and MDS. We are selecting patients for our clinical trials based on high levels of *RARA* gene expression. We are aware of several new drugs approved by the FDA since 2018 for the treatment of newly diagnosed unfit AML or patient subsets within newly diagnosed unfit AML (including ivosidenib, venetoclax, and glasdegib), and one new drug approved by the FDA in 2020 for the treatment of MDS or patient subsets within MDS (decitabine/cedazuridine). Tamibarotene may also face competition from other agents currently in clinical development for AML and MDS, including those in late-stage development from Gilead Sciences, Inc., Abbvie Inc., Roche Holding AG, Novartis AG, Astex Pharmaceuticals, Inc., and Pfizer Inc. We are not aware of any selective RAR α agonist programs that are in active clinical development.

SY-2101

We are developing SY-2101, a novel oral form of ATO, in patients with newly diagnosed APL. SY-2101 may face competition from Trisenox® or any of the generic forms of Trisenox, an intravenously administered arsenic trioxide product approved by the FDA for the treatment of APL. We are also aware of a traditional Chinese medicine (TCM)-based formulation of oral arsenic commercially available in China. In addition, we are aware of an oral formulation of arsenic trioxide in clinical development by Phebra Pty Ltd, or Phebra, an Australian based specialty pharmaceutical group. Phebra has entered into an agreement with Medsenic SAS, a European biopharmaceutical company, for the investigation of their oral arsenic trioxide compound for the treatment of autoimmune diseases. We are also aware of an oral formulation of arsenic trioxide being studied in an academic setting in Hong Kong.

We are conducting a Phase 1 clinical trial of SY-5609 in patients with select advanced solid tumors. We are aware of selective CDK7 inhibitors being developed in early clinical trials by Carrick Therapeutics Ltd., Exelixis, Inc. and Quriient Co. Ltd., as well as other selective CDK7 inhibitor programs that we believe are in preclinical development from Yungjin Pharma Co., Ltd., The Translational Genomics Research Institute, Applied Pharmaceutical Science, Inc. and Kirilys Therapeutics, Inc., and a collaboration between Exscientia Ltd. and GT Apeiron Therapeutics Ltd. focused on developing novel CDK inhibitors, including selective CDK7 inhibitors. SY-5609 may face competition from these CDK7 inhibitors. There is also significant competition from products with mechanisms other than CDK7 inhibition in pancreatic cancer and BRAF-mutant colorectal cancer, the disease areas where we are currently focusing our development of SY-5609.

Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions such as the European Union, or EU, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of biopharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Approval and Regulation of Drugs in the United States

In the United States, drug products are approved and regulated under the Federal Food, Drug and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. A company, institution or organization which takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor. The failure of a sponsor to comply with the applicable regulatory requirements at any time during the product development process may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions.

Specifically, a sponsor seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- design of a clinical protocol and submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency and purity of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;
- preparation and submission to the FDA of an NDA for a drug product which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labelling for one or more proposed indication(s);
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;

- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;
- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies

Before a sponsor begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND and are generally referred to as IND-enabling studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards and the United States Department of Agriculture's Animal Welfare Act, if applicable. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

An IND is a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, sponsors must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, must be submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee, or DSMB. This group provides a recommendation as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called “compassionate use,” is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

There is no obligation for a sponsor to make its investigational products available for expanded access. Sponsors of one or more investigational drugs for the treatment of a serious disease(s) or condition(s) must, however, make publicly available their policy for evaluating and responding to requests for expanded access for individual patients.

In addition, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator in accordance with GCP requirements which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may also be required after approval.

Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the investigational drug product’s pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.

Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage and dosage schedule. Multiple *Phase 2* clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly *Phase 3* clinical trials. *Phase 2* clinical trials are well controlled, closely monitored and conducted in a limited patient population.

Phase 3 clinical trials proceed if the *Phase 2* clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. *Phase 3* clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust *Phase 3* clinical trial may be designed to deliver the data that regulatory authorities will use to decide whether to approve, and, if approved, how to appropriately label a drug: such *Phase 3* studies are referred to as “pivotal.”

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate’s safety and effectiveness after approval. Such post-approval trials are typically referred to as *Phase 4* clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting *Phase 4* clinical trials could result in withdrawal of approval for products.

In March 2022, the FDA finalized guidance entitled “Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics,” which outlines how sponsors can utilize an adaptive trial design in the early stages of oncology product development (i.e., the first-in-human clinical trial) to compress the traditional three phases of trials into one continuous trial called an expansion cohort trial. Information to support the design of individual expansion cohorts are included in IND applications and assessed by the FDA. Expansion cohort trials can potentially bring efficiency to product development and reduce developmental costs and time. Progress reports detailing the status and a brief description of available results of the clinical trials must be submitted at least annually to the FDA. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

In December 2022, with the passage of the Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each *Phase 3* clinical trial or any other “pivotal study” of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, action plans must include the sponsor’s goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans.

Sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health, or NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. The failure to submit clinical trial information to clinicaltrials.gov, as required, is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to \$10,000 for each day the violation continues. Although the FDA has historically not enforced these reporting requirements due to the long delay in issuing final implementing regulations by the Department of Health and Human Services, or HHS, those regulations have now been issued and the FDA has issued several Notices of Noncompliance to manufacturers since April 2021.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the investigational drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Review and Approval of an NDA

In order to obtain approval to market a drug product in the United States, a marketing application must be submitted to the FDA that provides sufficient data establishing the safety, purity and potency of the proposed drug product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety, purity and potency of the drug product to the satisfaction of the FDA.

The NDA is a vehicle through which sponsors formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2023 is approximately \$3.25 million for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for federal fiscal year 2023 is approximately \$394,000. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

Following submission of an NDA, the FDA conducts a preliminary review of the application within 60 days of receipt and must inform the sponsor by that time whether the application is sufficiently complete to permit substantive review. If not, the FDA will issue a Refuse to File, or RTF, determination to the sponsor. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs, but the review process and the Prescription Drug User Fee Act, or PDUFA, goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission.

In connection with its review of an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications.

Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. With the passage of FDORA, Congress clarified the FDA's authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to the FDA, as well as other persons holding study records or involved in the study process.

In addition, as a condition of approval, the FDA may require a sponsor to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events and whether the product is a new molecular entity.

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy and Priority Review

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs, as applicable to our business, are referred to as fast track designation, breakthrough therapy designation and priority review designation. None of these programs changes the standards for approval but each may help expedite the development or approval process governing product candidates.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long, and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with priority review.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to initiate expedited proceedings to withdraw approval of the product. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

With the passage of FDORA, in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded; to require a sponsor of a product granted accelerated approval to submit progress reports on its post-approval studies to the FDA every six months until the study is completed; and to use expedited procedures to withdraw accelerated approval of an NDA or BLA after the confirmatory trial fails to verify the product's clinical benefit. Further, FDORA requires the agency to publish on its website "the rationale for why a post-approval study is not appropriate or necessary" whenever it decides not to require such a study upon granting accelerated approval.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter, or CRL. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

An approval letter authorizes commercial marketing of the product with specific prescribing information for each indication. If the FDA approves a new product, it may limit the approved indications for use of the product. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. The PREVENT Pandemics Act, which was enacted in December 2022, clarifies that foreign drug manufacturing establishments are subject to registration and listing requirements even if a drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States prior to being imported or offered for import into the United States.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in

addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug product.

In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. Further, with passage of the Pre-Approval Information Exchange Act, or the PIE Act, in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Previously, such communications were permitted under FDA guidance, but the new legislation explicitly provides protection to sponsors who convey certain information about products in development to payors, including unapproved uses of approved products.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the DOJ, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, or PREA, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The sponsor, the FDA, and the FDA's internal review

committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the sponsor may request an amendment to the plan at any time.

The FDA Reauthorization Act of 2017 established new requirements to govern certain molecularly targeted cancer indications. Any company that submits an NDA three years after the date of enactment of that statute must submit pediatric assessments with the NDA if the drug is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. The investigation must be designed to yield clinically meaningful pediatric study data regarding the dosing, safety and preliminary efficacy to inform pediatric labeling for the product.

The law now requires the FDA to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an “orphan drug” if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must seek orphan drug designation before submitting an NDA for the product candidate. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor’s marketing application for the same drug for the same condition for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different conditions. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Under Omnibus legislation signed by former President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drug products that received orphan drug designation before enactment of amendments to the FDCA in 2017 but have not yet been approved by the FDA.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term “same disease or condition” in the statute means the designated “rare disease or condition” and could not be interpreted by the FDA to mean the “indication or use.” Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing patent or regulatory exclusivity, including the non-patent and orphan exclusivity, for drug products. For biologic products, only non-patent exclusivity is extended. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA’s request, the additional

protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies that must contain substantial evidence of the safety and efficacy of the proposed new product for the proposed use. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the sponsor to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the sponsor for approval of the application "were not conducted by or for the sponsor and for which the sponsor has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the sponsor. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new product candidate for all or some of the label indications for which the referenced drug has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs.

Specifically, in order for an abbreviated new drug application, or ANDA, to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. This interpretation of the FDCA by the FDA was confirmed with enactment of the Ensuring Innovation Act in April 2021. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. The FDA's regulations governing patent listings were largely codified into law with enactment of the Orange Book Modernization Act in January 2021. When an ANDA or 505(b)(2) applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of the IND and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

FDA Approval and Regulation of Companion Diagnostics

If safe and effective use of a therapeutic depends on an *in vitro* diagnostic, then the FDA generally will require approval or clearance of that diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and *in vitro* companion diagnostics. According to the guidance, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic device is not approved or cleared for that indication.

Under the FDCA, *in vitro* diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA approval.

The FDA previously has required *in vitro* companion diagnostics intended to select the patients who will respond to the product candidate to obtain pre-market approval, or PMA, simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the sponsor must prepare and

provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee. For federal fiscal year 2023, the standard fee is \$441,547 and the small business fee is \$110,387.

Healthcare Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state health care laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make, improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment; and
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, and other healthcare providers, as well as ownership and investment interests held by physicians, and their immediate family members.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by the Health Insurance Portability and Accountability Act of 1996, or HIPAA, thus complicating compliance efforts.

Pharmaceutical Insurance Coverage and Healthcare Reform

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated health care costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for the product. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of health care costs also has become a priority of federal, state and foreign governments and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and biologics and other medical products, government control and other changes to the health care system in the United States. In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. In December 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseparable feature of the ACA, and therefore because the mandate was repealed as part of the Tax

Act, the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court heard this case and in June 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the ACA. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. The implementation of the rule was delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation, and was subsequently delayed until January 1, 2026 by the Infrastructure Investment and Jobs Act.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for

taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated \$4,000 a year in 2024 and, thereafter beginning in 2025, at \$2,000 a year.

At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Regulations and Procedures Governing Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, a sponsor will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the EU, generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

On January 31, 2022, the new Clinical Trials Regulation (EU) No 536/2014 became effective in the European Union and replaced the prior Clinical Trials Directive 2001/20/EC. The new regulation aims at simplifying and streamlining the authorization, conduct and transparency of clinical trials in the European Union. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial to be conducted in more than one Member State of the European Union, or EU Member State, will only be required to submit a single application for approval. The submission will be made through the Clinical Trials Information System, a new clinical trials portal overseen by the EMA and available to clinical trial sponsors, competent authorities of the EU Member States and the public.

The main characteristics of the new regulation include a single set of documents to be prepared and submitted for the application, as well as simplified reporting procedures for clinical trial sponsors, and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

The new regulation did not change the preexisting requirement that a sponsor must obtain prior approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the sponsor may only start a clinical trial at a specific study site after the applicable ethics committee has issued a favorable opinion.

Parties conducting certain clinical trials must, as in the United States, post clinical trial information in the EU at the EudraCT website: <https://eudract.ema.europa.eu>.

In March 2016, the European Medicines Agency, or EMA, launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRiority MEDicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted.

Marketing Authorization

To obtain a marketing authorization for a product under EU regulatory systems, a sponsor must submit an MAA either under a centralized procedure administered by the EMA, or one of the procedures administered by competent authorities in the EU Member States (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to a sponsor established in the EU. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, sponsors must demonstrate compliance with all measures included in an EMA-approved Paediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (i) a product-specific waiver, (ii) a class waiver or (iii) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area (i.e., the EU as well as Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products, and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure may at the request of the sponsor also be used in certain other cases. We anticipate that the centralized procedure will be mandatory for the product candidates we are developing.

Under the centralized procedure, the CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days, but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of EU law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product the European Commission must consult the Standing Committee on Medicinal Products for Human Use. The Standing Committee is composed of representatives of the EU Member States and chaired by a non-voting European Commission representative. The European Parliament also has a related “droit de regard.” The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The European Commission may grant a so-called “marketing authorization under exceptional circumstances.” Such authorization is intended for products for which the sponsor can demonstrate that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the sponsor cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information. Consequently, marketing authorization under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

- the sponsor must complete an identified program of studies within a time period specified by the competent authority, the results of which form the basis of a reassessment of the benefit/risk profile;
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by an authorized person; and
- the package leaflet and any medical information must draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents sponsors for authorization of generics of these innovative products from referencing the innovator’s data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator’s data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. The European Commission or the competent authorities of the EU Member States may decide on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid.

Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a drug can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (i) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (ii) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the sponsor must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States and a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the

same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated based on available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Regulatory Requirements after a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include compliance with the EU's stringent pharmacovigilance or safety reporting rules must be ensured, and the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU, and the marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, which are strictly regulated in the EU notably under Directive 2001/83EC, as amended, and EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the EU provides options for its Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Member States may approve a specific price for a product, or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other Member States allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various Member States, and parallel trade, i.e., arbitrage between low-priced and high-priced Member States, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Approval of Companion Diagnostic Devices

In the European Union, medical devices such as companion diagnostics must comply with the General Safety and Performance Requirements, or SPRs, detailed in Annex I of the EU Medical Devices Regulation (Regulation (EU) 2017/745), or MDR which came into force on May 26, 2021 and replaced the previously applicable EU Medical Devices Directive (Council Directive 93/42/EEC). Compliance with SPRs and additional requirements applicable to companion medical devices are prerequisites to be able to affix the CE Mark of Conformity to medical devices, without which they cannot be marketed or sold. To demonstrate compliance with the SPRs, a manufacturer must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. The MDR is meant to establish a uniform, transparent, predictable, and sustainable regulatory framework across the EU for medical devices.

Separately, the regulatory authorities in the EU also adopted a new In Vitro Diagnostic Regulation, or IVDR, (EU) 2017/746, which became effective in May 2022. The new regulation replaces the In Vitro Diagnostics Directive (IVDD) 98/79/EC. Manufacturers wishing to apply to a notified body for a conformity assessment of their in vitro diagnostic medical device had until May 2022 to update their Technical Documentation to meet the requirements and comply with the new, more stringent Regulation. The regulation, among other things, strengthens the rules on placing devices on the market and reinforces surveillance once they are available; establishes explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance, and safety of devices placed on the market; improves the traceability of medical

devices throughout the supply chain to the end-user or patient through a unique identification number; sets up a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the European Union; and strengthens rules for the assessment of certain high-risk devices, such as implants, which may have to undergo an additional check by experts before they are placed on the market.

General Data Protection Regulation

There are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area, or the EEA, and the processing of personal data that takes place in the EEA, is subject to the EU's General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, and it imposes heightened requirements on companies that process health and other sensitive data, such as requiring in many situations that a company obtain the consent of the individuals to whom the sensitive personal data relate before processing such data. Examples of obligations imposed by the GDPR on companies processing personal data that fall within the scope of the GDPR include providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, appointing a data protection officer, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EEA, including the U.S., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield framework, or Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U.S. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the U.S. While we were not self-certified under the Privacy Shield, this CJEU decision may lead to increased scrutiny on data transfers from the EU to the U.S. generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

On June 23, 2016, the electorate in the U.K. voted in favor of leaving the EU, commonly referred to as Brexit. As with other issues related to Brexit, there are open questions about how personal data will be protected in the U.K. and whether personal information can transfer from the EU to the U.K. Following the withdrawal of the U.K. from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR. While the Data Protection Act of 2018 in the U.K. that "implements" and complements the GDPR has achieved Royal Assent on May 23, 2018 and is now effective in the U.K., it is unclear whether transfer of data from the EEA to the U.K. will remain lawful under the GDPR. The U.K. government has already determined that it considers all European Union 27 and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the U.K. to the EU/EEA remain unaffected. In addition, a recent decision from the European Commission appears to deem the U.K. as being "essentially adequate" for purposes of data transfer from the EU to the U.K., although this decision may be re-evaluated in the future.

Additionally, in October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-US Privacy Shield. The EC initiated the process to adopt an adequacy decision for the EU-US Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

Beyond the GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow the GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and any eventual sale and distribution of commercial products.

Sales and Marketing

We hold North American, European, Central and South American, Australian, Israeli and Russian commercialization rights to tamibarotene for all cancer indications, and worldwide rights to SY-2101 and SY-5609 and all of our other preclinical programs, other than our sickle cell disease program in which we are collaborating with GBT, for all potential indications. With respect to our sickle cell disease program, GBT has the option to obtain exclusive commercialization rights to products containing compounds arising out of the collaboration for all uses. If GBT exercises its option, we have a co-promotion right in the United States with respect to the first such product.

Subject to receiving marketing approval, we intend to build a focused sales and marketing organization in the United States to sell our products. We believe that such an organization will be able to address the community of physicians who are key specialists in treating the patient populations for which our product candidates are being developed. We also plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with researchers and practitioners in relevant fields of medicine.

Where appropriate, we may elect to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products. In certain instances, we may consider building our own commercial infrastructure.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates. Although we intend to rely on third-party contract manufacturers to produce our product candidates and any products we may develop in the future, we have recruited personnel with experience to manage these third-party contract manufacturers.

Employees

As of December 31, 2022, we had 117 full-time employees and one part-time employee, including 52 employees with M.D., Ph.D. or Pharm.D. degrees. Of these full-time employees, 89 employees are engaged in research and development activities and 28 employees are engaged in general and administrative activities. During the year ended December 31, 2022, we hired 35 new employees, of whom 26 are engaged in research and development activities and nine are engaged in general and administrative activities. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We conduct an employee engagement survey every year and, based on the results of the survey, we consider our relationship with our employees to be good. We focus on employee recruiting and attrition rates and our progress against equity, diversity and inclusion goals as key human capital measures in managing our business.

Corporate Information

We were incorporated under the laws of the State of Delaware on November 9, 2011 under the name LS22, Inc. We changed our name to Syros Pharmaceuticals, Inc. on August 15, 2012.

Information Available on the Internet

Our Internet website address is www.syros.com. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report. We have included our website address in this in this Annual Report solely as an inactive textual reference. We make available free of charge through our website our Annual Report, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through the “SEC Filings” section of our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. We also make available, free of charge on our website, the reports filed with the U.S. Securities and Exchange Commission, or SEC, by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. You can review our electronically filed reports and other information that we file with the SEC on the SEC’s website at <http://www.sec.gov>.

ITEM 1A. RISK FACTORS

We operate in a dynamic and rapidly changing business environment that involves multiple risks and substantial uncertainty. The following discussion addresses risks and uncertainties that could cause, or contribute to causing, actual results to differ from expectations in material ways. In evaluating our business, investors should carefully consider the risks described below in addition to the other information set forth in this Annual Report on Form 10-K, or Annual Report, including the Management's Discussion and Analysis of Financial Condition and Results of Operations section and the consolidated financial statements and related notes. These risks, some of which have occurred and any of which may occur in the future, can have a material adverse effect on our business, financial condition, results of operations or the price of our publicly traded securities. The risks described below are not the only risks we face. Additional risks and uncertainties not currently known to us, or that we currently deem to be immaterial, may occur or become material in the future and adversely affect our business, reputation, financial condition, results of operations or the price of our publicly traded securities. Therefore, historical operating results, financial and business performance, events and trends are often not a reliable indicator of future operating results, financial and business performance, events or trends. If any of the following risks occurs, our business, financial condition, and results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception, expect to incur significant and increasing losses for at least the next several years, and may never achieve or maintain profitability.

We have incurred significant annual net operating losses in every year since our inception. We expect to continue to incur significant and increasing net operating losses for at least the next several years. Our net losses were \$94.7 million, \$86.6 million, and \$84.0 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of \$558.2 million. We have not generated any revenues from product sales, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. We have financed our operations to date primarily through the sale of equity securities. We have devoted substantially all of our financial resources and efforts to research and development and general and administrative expense to support such research and development. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital.

We anticipate that our future funding requirements, both short-term and long-term, will depend on many factors and will increase substantially if and as we:

- continue our planned clinical development activities with respect to tamibarotene, SY-2101 and SY-5609;
- develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with our products and product candidates;
- initiate and continue research, preclinical and clinical development efforts for our research and preclinical programs;
- seek to identify and develop additional product candidates, which may involve entering into collaborations, licensing agreements or other arrangements;
- acquire or in-license other product candidates or technologies;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical trials, if any;
- establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize various products for which we may obtain marketing approval, if any;
- become obligated to make milestone payments upon the successful completion of specified development and commercialization activities;

- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio; and
- hire and retain additional personnel and add operational, financial and management information systems, including personnel and systems to support our product development and commercialization efforts.

Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are, or any collaborator is, able to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. Successful commercialization will require achievement of key milestones, including initiating and successfully completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling products for which marketing approval has been obtained, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues, and if or when we might achieve profitability. We may never succeed in these activities and, even if we do, or any collaborators do, we may never generate revenues that are large enough for us to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or continue our operations and cause a decline in the value of our common stock.

We will need substantial additional funding to execute our operating plan, and if we are unable to raise capital, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a time consuming, expensive and uncertain process. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We believe that our cash, cash equivalents and marketable securities as of December 31, 2022 will enable us to fund our planned operating expense and capital expenditure requirements into the second quarter of 2025. Our estimate as to how long we expect our existing cash, cash equivalents, and marketable securities to be able to continue to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. In any event, our existing cash, cash equivalents and marketable securities will not be sufficient to fund all of the efforts that we plan to undertake or to fund the completion of development of all of our product candidates.

Our future funding requirements will depend on many factors, including those discussed above under “*We have incurred significant losses since inception, expect to incur significant and increasing losses for at least the next several years, and may never achieve or maintain profitability.*” Our future funding requirements may also depend on:

- whether a drug candidate will be nominated to enter into investigational new drug application-enabling studies under our sickle cell disease collaboration with GBT, whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U.S. co-promotion option under the GBT agreement;
- whether our target discovery collaboration with Incyte will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the collaboration agreement with Incyte will ever be paid;
- the costs of precommercial activities related to our product candidates, including any physician education programs relating to selecting and treating genomically defined patient populations;

- the timing and amount of milestone and other payments due to TMRC Co. Ltd., or TMRC, associated with the development, manufacture and commercialization of tamibarotene;
- the timing and amount of milestone payments due to Orsenix, LLC, associated with the development and commercialization of SY-2101; and
- the timing and amount of milestone payments due to Qiagen Manchester Limited associated with the development and commercialization of a companion diagnostic test for use with tamibarotene.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

Global credit and financial markets have experienced extreme volatility and disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability, including most recently in connection with the impacts of COVID-19, disruptions impacting global supply, the conflict between Russia and Ukraine and related sanctions against Russia, increasing inflation rates and interest rate changes. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Furthermore, our stock price may decline due in part to the volatility of the stock market and the general economic downturn.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We expect our expenses to remain high in connection with our planned operations. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, as we did through a private placement of our securities in September 2022, the ownership interests of our existing stockholders may be substantially diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect our stockholders' rights. In addition, debt financing, such as our term loan facility with Oxford that we entered into in February 2020, has created fixed payment obligations and imposed restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, such as our collaboration agreement with GBT, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. In this regard, we recently announced that we are seeking a partnership for the clinical development of SY-5609, and that we are seeking partnerships for our oncology discovery programs, including our CDK12 program. However, we cannot provide assurance that these transactions will be consummated, or that sufficient additional capital to support the further development of SY-5609 or of our oncology discovery programs can be obtained or will be obtained on favorable terms.

The terms of our Loan and Security Agreement place restrictions on our operating and financial flexibility.

In February 2020, we entered into a Loan and Security Agreement with Oxford, which is secured by substantially all of our currently owned or later acquired personal property other than our intellectual property (but including the right to payments and proceeds of intellectual property), which is subject to a negative pledge. We refer to the Loan and Security Agreement with Oxford as the Loan Agreement. We borrowed \$20.0 million upon execution of the Loan Agreement and borrowed an additional \$20.0 million term loan advance in December 2020. One additional term loan advance of \$20.0 million remains available under the Loan Agreement, subject to certain terms and conditions, including the achievement of certain milestones.

On July 3, 2022, we entered into an amendment to the Loan Agreement, or the Loan Amendment, pursuant to which Oxford, in its capacity as lender and agent, has agreed to modify the Loan Agreement in order to, among other things, (i) extend the interest only period from March 1, 2023 to March 1, 2024 and extend the maturity date from February 1, 2025 to February 1, 2026, and (ii) upon the achievement of certain milestones and subject to the payment of certain fees, further extend the interest only period to September 1, 2024 and maturity date to August 1, 2026.

The Loan Agreement, as amended by the Loan Amendment, contains representations and warranties, affirmative and negative covenants applicable to us and our subsidiaries and events of default, as more fully described in the Loan Agreement and Loan Amendment. In particular, the Loan Agreement also includes events of default, the occurrence and during the continuation of which provide Oxford, as collateral agent, with the right to exercise remedies against us and the collateral securing the loans under the Loan Agreement, including foreclosure against our property securing the Loan Agreement, including our cash, potentially requiring us to renegotiate our agreement on terms less favorable to us, or to immediately cease operations.

Further, if we are liquidated, the lenders' right to repayment would be senior to the rights of the holders of our common stock to receive any proceeds from the liquidation. Oxford could declare a default upon the occurrence of any event that they interpret as a material adverse change as defined under the Loan Agreement, thereby requiring us to repay the loan immediately or to attempt to reverse the declaration of default through negotiation or litigation. Any declaration by Oxford of an event of default could significantly harm our business and prospects and could cause the price of our common stock to decline.

Risks Related to the Discovery, Development and Commercialization of Product Candidates

Our approach to the discovery and development of product candidates is novel and unproven, and we do not know whether we will be able to develop any products of commercial value.

We are primarily focused on developing medicines for the treatment of hematologic malignancies. Tamibarotene, our lead product candidate, is being evaluated in genomically defined patients whose diseases have not been adequately addressed to date by other genomics approaches. While we believe that targeting this genomically defined patient population may potentially lead to a higher likelihood of clinical success, our approach is both novel and unproven, and our efforts may not result in the development of commercially viable medicines. We may also be incorrect about the effects of our product candidates on the diseases of genomically defined patient populations, which may limit the utility of our approach or the perception of the utility of our approach. For example, we have not yet succeeded and may never succeed in demonstrating efficacy and safety for our current or any future product candidates in a pivotal clinical trial or in obtaining marketing approval thereafter. Furthermore, our estimates of genomically defined patient populations available for study and treatment may be lower than expected, which could adversely affect our ability to conduct clinical trials and may also adversely affect the size of any market for medicines we may successfully commercialize.

In the near term, we are dependent on the success of tamibarotene, SY-2101 and SY-5609. If we are unable to initiate or complete the clinical development of, obtain marketing approval for or successfully commercialize tamibarotene, SY-2101 or SY-5609, either alone or with a collaborator, or if we experience significant delays in doing so, our business could be substantially harmed.

We currently have no products approved for sale and are investing a significant portion of our efforts and financial resources in the development of tamibarotene, SY-2101 and SY-5609. Our ability to generate product revenue will depend heavily on the successful clinical development and eventual commercialization of our current and any future product candidates, such as tamibarotene, SY-2101 and SY-5609.

We, and any collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements in foreign jurisdictions. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans.

Clinical trials of a new product candidate require the activation of clinical trial sites and the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Our anticipated time to data in our clinical trials and the quantity of data to be presented from these trials is and will continue to be subject to our continued ability to activate clinical trial sites, recruit

eligible patients, and the satisfaction by patients of other eligibility criteria for participation in the trial. In the case of tamibarotene, our time to data is also dependent on the prevalence of patients who overexpress the *RARA* biomarker and the impact of new product approvals in the AML and MDS fields. The rate of site activations and patient enrollment in the trial is difficult to predict, and we have experienced slower-than-anticipated site activations in our SELECT-MDS-1 trial as we expanded the study global footprint. There can be no assurance that we will enroll or have data from our clinical trials when we anticipate.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development. Moreover, we, or any collaborators, may experience any of a number of possible unforeseen adverse events in connection with clinical trials, many of which are beyond our control, including:

- we, or our collaborators, may fail to demonstrate efficacy in a clinical trial or across a broad population of patients;
- it is possible that, even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. For example, many compounds that initially showed promise in earlier stage testing have later been found to cause side effects that prevented further development of the compound;
- our product candidates may have undesirable side effects or other unexpected characteristics or otherwise expose participants to unacceptable health risks, causing us, our collaborators or our investigators, regulators or institutional review boards or the data safety monitoring board for such trial to halt, delay, interrupt, suspend or terminate the trials or cause us, or any collaborators, to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective;
- if our product candidates have undesirable side effects, it could result in a more restrictive label, or it could result in the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities;
- clinical trials of our product candidates may produce negative or inconclusive results, and we, or our collaborators, may decide, or regulators may require us, to conduct additional clinical trials, including testing in more subjects, or abandon product development programs;
- regulators or institutional review boards may not authorize us, our collaborators or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we or our collaborators may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate; enrollment in these clinical trials, which may be particularly challenging for some of the diseases we target, may be slower than we anticipate; or participants may drop out of these clinical trials at a higher rate than we anticipate;
- third-party contractors used by us or our collaborators may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all;
- significant preclinical study or clinical trial delays could shorten any periods during which we, or any collaborators, may have the exclusive right to commercialize our product candidates or allow our

competitors, or the competitors of any collaborators, to bring products to market before we, or any collaborators, do;

- the cost of clinical trials of our product candidates may be greater than anticipated; and

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate.

In addition, we are conducting our SELECT-MDS-1 clinical trial in foreign countries and may conduct other clinical trials outside the United States in the future. We do not have employees or significant operational capabilities located outside of the United States, and we rely on third parties, such as contract research organizations, or CROs, to conduct our clinical trials in foreign countries. Conducting clinical trials in foreign countries presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocols as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

Our failure to successfully begin and complete clinical trials of our product candidates, including tamibarotene, SY-2101 and SY-5609, and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates could result in additional costs to us, or any collaborators, would impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties and would significantly harm our business.

Adverse events or undesirable side effects caused by, or other unexpected properties of, product candidates that we develop may be identified during development and could delay or prevent their marketing approval or limit their use.

Side effects from product candidates undergoing clinical evaluation may be unpredictable. Tamibarotene has been observed to be associated with adverse events, such as mild or moderate dry skin, skin rash, headache and bone pain, as well as retinoic acid syndrome and elevated levels of cholesterol, lipids, liver function enzymes and white blood cells, which were severe in certain cases. Furthermore, retinoids such as tamibarotene may cause birth defects and therefore may carry a warning on their label. Other examples of retinoids, a class of chemical compounds that are related to vitamin A, include all trans retinoic acid (also known as ATRA), Retin-A, retinol (found in over-the-counter skin creams), isotretinoin and bexarotene. Additionally, SY-5609 has been observed to be associated with adverse events such as nausea, diarrhea, thrombocytopenia, fatigue and anemia. Furthermore, we have limited experience administering SY-2101 to humans, so the safety profile it will demonstrate in human clinical trials remains uncertain.

We cannot predict at this time whether the combination of our product candidates with another product, or with any premedication administered to mitigate potential side effects, will be well tolerated by patients in clinical studies or that any unexpected adverse events or undesirable side effects will not occur. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any collaborators, may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective.

Failure to successfully validate, develop and obtain regulatory approval for companion diagnostics could harm our drug development strategy.

As one of the key elements of our development strategy, we seek to identify genomically defined subsets of patients within a disease category who may derive benefit from the product candidates we are developing. In collaboration with partners, we plan to develop companion diagnostics to help us to more accurately identify patients within a particular subset, both during our clinical trials and in connection with the commercialization of our product candidates that we are developing or may in the future develop. Companion diagnostics are subject to regulation by the FDA and comparable foreign regulatory authorities as medical devices and require separate regulatory approval prior to commercialization. While our drug candidates will have their marketing applications reviewed by FDA's Center for Drug Evaluation and Research, or CDER, companion diagnostics require separate marketing applications under the primary jurisdiction of FDA's Center for Devices and Radiological Health, or CDRH. This parallel jurisdiction and separate marketing applications could result in coordination issues, require additional time and effort, or result in delays or failure to obtain marketing approval for either the companion diagnostic or related drug indications.

We do not develop companion diagnostics internally and thus we will be dependent on the sustained cooperation and effort of one or more third-party collaborators in developing, obtaining approval for, and commercializing these companion diagnostics. We and our collaborators may encounter difficulties in developing and obtaining approval for the companion diagnostics, including issues relating to selectivity/specificity, analytical validation, reproducibility, or clinical validation. For example, if we are to succeed in obtaining regulatory approval for a companion diagnostic to identify genomically defined subsets of patients with AML or MDS using our *RARA* biomarker, we will need to demonstrate to regulatory authorities that *RARA* biomarker selection is associated with a response to tamibarotene. In March 2022, we entered into a Master Collaboration Agreement and associated project work plan with Qiagen, pursuant to which Qiagen will develop and commercialize a companion diagnostic for this biomarker. Any delay or failure by us, Qiagen, or any future collaborators to develop or obtain regulatory approval of the companion diagnostics could delay or prevent approval of our product candidates, delay the commercialization of our product candidates, or diminish the likelihood of achieving the commercial potential for our product candidates. In addition, Qiagen or any future collaborators may encounter production difficulties that could constrain the supply of the companion diagnostics, and both they and we may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community. If such companion diagnostics fail to gain market acceptance, it would have an adverse effect on our ability to derive revenues from sales, if any, of our products. In addition, Qiagen or any other companion diagnostic collaborator with whom we contract may decide not to commercialize or to discontinue selling or manufacturing the companion diagnostic that we anticipate using in connection with development and commercialization of our product candidates, or our relationship with such collaborator may otherwise terminate. We may not be able to enter into arrangements with another provider to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our product candidates.

If we, or any collaborators, experience delays or difficulties in the enrollment of patients in clinical trials, our or their receipt of necessary regulatory approvals could be delayed or prevented.

We, or any collaborators, may not be able to initiate or continue clinical trials for our current product candidates or any future product candidates that we, or any collaborators, may develop if we, or they, are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including the size and nature of the patient population, the severity of the disease under investigation, and the availability of approved or investigational therapeutics for the relevant disease, the proximity of patients to clinical sites, the eligibility criteria for and design of the trial, efforts to facilitate timely enrollment, competing clinical trials, clinicians' and patients' perceptions as to the potential advantages and risks of the drug being studied in relation to other available therapies, and actual or threatened public health emergencies and outbreaks of disease (including, for example, the COVID-19 pandemic). In addition, patients that enroll may subsequently be dropped from the clinical trial due to having misrepresented their eligibility to participate or due to non-compliance with clinical trial protocol, resulting in the need to increase the enrollment size for the clinical trial or extend the clinical trial's duration.

In particular, we intend to enrich certain of our clinical trials with patients most likely to respond to our product candidates. Genomically defined diseases may, however, have relatively low prevalence and it may be difficult for us or third parties with whom we collaborate to identify patients for our trials, which may lead to delays in enrollment for our trials. We intend to develop, or engage third parties such as Qiagen to develop, companion diagnostics for use in our clinical trials, but we or such third parties may not be successful in developing such companion diagnostics, furthering the difficulty in identifying genomically defined subsets of patients for our clinical trials. Moreover, in light of the recent approval of new products for the treatment of AML, there is substantial competition for patients to be enrolled in clinical trials for this disease. Our inability, or the inability of any collaborators, to enroll a sufficient number of patients for our, or their, clinical trials could result in significant delays or may require us or them to abandon one or more clinical trials altogether. Enrollment delays in our, or their, clinical trials may result in increased development costs for our product candidates, delay or halt the development of and approval processes for our product candidates and jeopardize our, or any collaborators', ability to commence sales of and generate revenues from our product candidates, which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

Results of preclinical studies and early clinical trials may not be predictive of results of future or late-stage clinical trials.

We cannot assure you that we will be able to replicate in human clinical trials the results we observed in earlier studies. Moreover, the outcome of preclinical studies and early clinical trials may not be predictive of the success of later or late-stage clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many

companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for our current product candidates or any future product candidates that we, or any collaborators, may develop.

We have never obtained marketing approval for a product candidate. It is possible that the FDA may refuse to accept for substantive review any new drug applications, or NDAs, that we submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA does not accept or approve our NDAs for any of our product candidates, it may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA-required trials or studies, approval of any NDA or application that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDAs. In addition, our development programs contemplate the development of companion diagnostics by our third-party collaborators, such as Qiagen. Companion diagnostics are subject to regulation as medical devices and must themselves be approved for marketing by the FDA or certain other foreign regulatory agencies before we may commercialize our product candidates.

Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing our product candidates or any companion diagnostics, generating revenues and achieving and sustaining profitability. If any of these outcomes occur, we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

Even if any product candidates that we, or any collaborators, may develop receive marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborators, to market the product.

Clinical trials of tamibarotene, SY-2101 or SY-5609 or any future product candidates that we, or any collaborators, may develop will be conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any collaborators, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, we could be subject to the withdrawal of prior regulatory approvals and/or the imposition of additional regulatory requirements, restrictions on manufacturing, labelling and marketing, and product recalls. In addition, we or any collaborators could be sued and held liable for harm caused to patients and could become subject to fines, injunctions or the imposition of civil or criminal penalties. Any of these events could harm our reputation, business and operations and could negatively impact our stock price.

Even if our current product candidates, or any future product candidate that we, or any collaborators, may develop receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, in which case we may not generate significant revenues or become profitable.

We have never commercialized a product, and even if one of our product candidates is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including the efficacy and safety of the product, the potential advantages of the product compared to competitive therapies, the prevalence and severity of any side effects, whether the product is designated under physician treatment guidelines as a first-, second- or third-line therapy, our ability, or the ability of any collaborators, to offer the product for sale at competitive prices, the product's convenience and ease of administration compared to alternative treatments, the willingness of the target patient population to try, and of physicians to prescribe, the product, limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling, the strength of sales, marketing and distribution support, changes in the standard of care for the targeted indications for the product; and the availability and amount of coverage and reimbursement from government payors, managed care plans and other third-party payors.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for marketing approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. In this regard, we announced in November 2022 that we have elected to seek a partnership for the further development of SY-5609.

Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution arrangements with third parties, we may not be successful in commercializing any product candidates if approved.

We do not have a sales, marketing or distribution infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We plan to build focused capabilities to commercialize development programs for certain indications where we believe that the medical specialists for the indications are sufficiently concentrated to allow us to effectively promote the product with a targeted sales team. The development of sales, marketing and distribution capabilities will require substantial resources, will be time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we could have prematurely or unnecessarily incurred these commercialization costs. This may be costly, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

In certain indications, we plan to seek to enter into collaborations that we believe may contribute to our ability to advance development and ultimately commercialize our product candidates. We also intend to seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

If we do not establish sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates that receive marketing approval.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

We expect that we, and any collaborators, will face significant competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide with respect to any of our product candidates that we, or any collaborators, may seek to develop or commercialize in the future. Specifically, there are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of product candidates for the treatment of the key indications of our most advanced programs.

For example, we are aware of several new drugs approved by the FDA since 2018 for the treatment of newly diagnosed unfit AML or patient subsets within newly diagnosed unfit AML (including ivosidenib, venetoclax, and glasdegib), and one new drug approved by the FDA in 2020 for the treatment of MDS or patient subsets within MDS (decitabine/cedazuridine). Tamibarotene may also face competition from other agents currently in clinical development for AML and MDS, including those in late-stage development from Gilead Sciences, Inc., Abbvie Inc., Roche Holding AG, Novartis AG, Astex Pharmaceuticals, Inc. and Pfizer Inc.

SY-2101 may face competition from Trisenox® or any of the generic forms of Trisenox, an IV ATO product approved by the FDA for the treatment of APL. We are also aware of a traditional Chinese medicine (TCM)-based formulation of oral arsenic commercially available in China. In addition, we are aware of an oral formulation of ATO in clinical development by Phebra Pty Ltd, or Phebra, an Australian based specialty pharmaceutical group. Phebra has entered into an agreement with Medsenic SAS, a European biopharmaceutical company, for the investigation of their oral ATO compound for the treatment of autoimmune diseases. We are also aware of an oral formulation of ATO being studied in an academic setting in Hong Kong.

In addition, we are aware of selective CDK7 inhibitors being developed in early clinical trials by Carrick Therapeutics Ltd., Exelixis, Inc. and Quriert Co. Ltd., as well as other selective CDK7 inhibitor programs that we believe are in preclinical development from Yungjin Pharma Co., Ltd., The Translational Genomics Research Institute, Applied Pharmaceutical Science, Inc. and Kirilys Therapeutics, Inc., and a collaboration between Exscientia Ltd. and GT Apeiron Therapeutics Ltd. focused on developing novel cyclin-dependent kinase, or CDK, inhibitors, including selective CDK7 inhibitors. SY-5609 may face competition from these CDK7 inhibitors. There is also significant competition from products with mechanisms other than CDK7 inhibition in pancreatic cancer and BRAF-mutant colorectal cancer, the disease areas where we are currently focusing our development of SY-5609.

Our competitors may succeed in developing, acquiring or licensing technologies and products that are more effective, have fewer side effects or more tolerable side effects, have greater ease of access, or are less costly than any product candidates that we are currently developing or that we may develop, which could render our product candidates obsolete and noncompetitive.

Our competitors may develop and commercialize products that are safer or more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we, or any collaborators, may develop. For example, the evolving standard of care for the treatment of patients with AML and the response rates and duration of response seen with approved and investigational agents in this disease may result in a longer and more complex clinical development path for tamibarotene, which in turn will impact the potential return on investments in clinical trials of tamibarotene. Our competitors also may obtain FDA or other marketing approval for their products before we, or any

collaborators, are able to obtain approval for ours, which could result in our competitors establishing a strong market position before we, or any collaborators, are able to enter the market.

Many of our existing and potential future competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining marketing approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, the development of our product candidates.

Even if we, or any collaborators, are able to commercialize any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, third-party payor reimbursement practices or healthcare reform initiatives, any of which could harm our business.

The commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third-party payors, including government health care programs and private health insurers. If coverage is not available, or reimbursement is limited, we, or any collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement levels for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time consuming and costly process that may require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any collaborators, to successfully commercialize any of our product candidates will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third-party payors. Third-party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of any collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of any collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or any collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be

based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we, or any collaborator, obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

We will face an inherent risk of product liability claims as a result of the clinical testing of our product candidates despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we or any collaborators commercially sell any product that we may or they may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in, among other consequences, decreased demand for our product candidates or products that we may develop, injury to our reputation and significant negative media attention, withdrawal of clinical trial participants, significant costs to defend resulting litigation, substantial monetary awards to trial participants or patients, loss of revenue, reduced resources of our management to pursue our business strategy, and the inability to commercialize any products that we may develop.

Although we maintain clinical trial liability insurance coverage in the amount of up to \$10.0 million in the aggregate, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if and when we commercialize any product that receives marketing approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business, financial condition, results of operations and prospects.

If the FDA or comparable foreign regulatory authorities approve generic versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a "reference-listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Manufacturers may seek approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug and that the generic version is bioequivalent to the reference-listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference-listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference-listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The FDCA provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. Because the composition

of matter patent for tamibarotene has expired and our license rights to tamibarotene from TMRC are limited to human cancer indications, it is possible that another applicant could obtain approval for a similar product from the FDA before us, in which case our NDA for tamibarotene would not be eligible for NCE exclusivity. See "*Risks Related to Our Intellectual Property—We do not have composition of matter patent protection with respect to tamibarotene or the active pharmaceutical ingredient of SY-2101.*" If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products may face from generic versions of our products could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates.

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct our clinical trials and certain aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including by failing to meet deadlines for the completion of such trials, research or testing.

We currently rely and expect to continue to rely on third parties such as consultants, clinical investigators, CROs, clinical data management organizations, medical institutions and other similar entities, to complete certain aspects of our preclinical testing and clinical trials and provide services in connection with such clinical trials. Any third parties on which we currently rely or may in the future rely may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities. We additionally rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our medicines, producing additional losses and depriving us of potential product revenue.

Our reliance on these third parties for research and development activities will reduce our control over these activities, but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our medicines.

We currently depend on third-party manufacturers to produce our preclinical and clinical drug supplies and we intend to rely upon third-party manufacturers to produce commercial supplies of any approved product candidates.

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third-party manufacturers for the manufacture of our product candidates for preclinical and clinical testing and for commercial supply of any of these product candidates for which we or our collaborators obtain marketing approval. We have engaged, and expect to continue engaging, third-party suppliers and manufacturers in China and India. Natural disasters such as earthquakes, tsunamis, power shortages or outages, floods or monsoons, public health crises such as the COVID-19 pandemic or other pandemics or epidemics, political crises such as terrorism, war, political insecurity or other conflict, or other events outside of our control could adversely affect the ability of these third parties to perform their obligations as expected.

We also do not currently have a long-term supply agreement with any third-party manufacturers. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, we face risks such as the possible breach of the agreement by the third party or termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient to us. We also face risks

associated with reliance on third parties for regulatory compliance, quality assurance, and safety and pharmacovigilance reporting.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or medicines, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business and results of operations.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply of bulk drug substance or drug product. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

We currently depend on a third-party manufacturer to develop and validate the clinical trial assay being used to select patients with our proprietary RARA biomarker, and if this assay does not perform as designed, our clinical trials of tamibarotene may be adversely affected.

We are currently conducting SELECT-MDS-1, a Phase 3 clinical trial evaluating tamibarotene in combination with azacitidine in HR-MDS patients who have been prospectively selected using our proprietary *RARA* biomarker, and SELECT-AML-1, a randomized Phase 2 clinical trial evaluating tamibarotene in combination with venetoclax and azacitidine in newly diagnosed patients with AML who are positive for *RARA* overexpression and are not suitable candidates for standard intensive chemotherapy. We collaborate with a third party with respect to the clinical trial assay being used to select patients with the *RARA* biomarker for inclusion in these trials. The FDA has approved an investigational device exemption for the assay being used to select patients with the *RARA* biomarker, and we used this assay in our earlier Phase 2 trial evaluating the safety and efficacy of tamibarotene in certain AML and MDS patient populations. Based on data from over 175 patients screened in our clinical trials, we believe approximately 50% of MDS patients and approximately 30% of AML patients are positive for *RARA* overexpression. Our ability to continue to prospectively select patients who overexpress *RARA* for SELECT-MDS-1 and SELECT-AML-1 depends on the ability of this clinical trial assay to identify suitable patients for these clinical trials. If this assay does not perform as designed, it could adversely affect our estimated timelines to enroll patients, or adversely impact the results of these trials, which could significantly harm our business and commercial prospects.

To the extent that we enter into collaborations with third parties for the development and commercialization of any product candidates, our prospects with respect to those product candidates will depend in significant part on the success of those collaborations.

We expect to enter into collaborations for the development and commercialization of one or more product candidates we may develop, as we have with GBT to develop novel therapies for sickle cell disease and beta thalassemia and with Incyte to identify new drug targets in the field of myeloproliferative neoplasms. To the extent we enter into such collaborations, we will have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on any collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving our product candidates pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- our collaboration agreements with GBT and Incyte contain, and any collaboration agreement that we enter into in the future may contain, restrictions on our ability to enter into potential collaborations, to conduct research or development in certain fields, or to otherwise develop specified product candidates;
- there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential collaborators; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If any collaborator of ours is involved in a business combination, it could decide to delay, diminish or terminate the development or commercialization of any product candidate licensed to it by us.

We are currently seeking, and we expect to continue to seek, to establish additional collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

We are currently seeking, and we expect to continue to seek, to establish one or more additional collaborators for the development and commercialization of one or more of our product candidates or to validate targets. For example, we are seeking partnership opportunities for our SY-5609 clinical program and for our oncology discovery programs. Likely collaborators may include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In addition, if we are able to obtain marketing approval for product candidates from foreign regulatory authorities, we intend to enter into strategic relationships with international biotechnology or pharmaceutical companies for the commercialization of such product candidates outside of the United States.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors. Those factors may include the potential differentiation of our product candidates from competing product candidates, design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and the potential of competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate.

We may not be able to negotiate new collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, such as SY-5609 or our oncology discovery programs, reduce or delay our development program or one or more of our other development programs, delay our potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense.

Risks Related to Our Intellectual Property

If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to our business.

We are party to several license agreements under which we license patent rights and other intellectual property related to our business, including the TMRC license agreement, pursuant to which we were granted a license under specified patent rights, data, regulatory filings and other intellectual property primarily for the North American and European development and commercialization of tamibarotene for the treatment of human cancer indications. We may enter into additional license agreements in the future. Our license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under these licenses, our licensors may have the right to terminate these license agreements, in which event we might not be able to market any product that is covered by these agreements, or our licensors may convert the license to a non-exclusive license, which could adversely affect the value of the product candidate being developed under the license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may also result in our having to negotiate new or reinstated licenses with less favorable terms.

We do not have composition of matter patent protection with respect to tamibarotene or the active pharmaceutical ingredient of SY-2101.

We own certain patents and patent applications with claims directed to specific methods of using tamibarotene and we expect to have marketing exclusivity from the FDA and EMA for a period of no less than five and ten years, respectively, because tamibarotene has not been approved in these markets. Composition of matter patent protection in the United States and elsewhere covering tamibarotene has expired, however. In addition, we do not have composition of matter patent protection for arsenic trioxide, the active pharmaceutical ingredient of SY-2101. We may be limited in our ability to list our method patents in the FDA's Orange Book if the use of our products, consistent with its FDA-approved label, would not fall within the scope of our patent claims. Also, our competitors may be able to offer and sell products so long as these competitors do not infringe any other patents that we (or third parties) hold, including patents with claims directed to the manufacture of tamibarotene and/or method of use patents, or to the formulation of SY-2101 drug product and/or methods of manufacture of SY-2101. In general, method of use patents are more difficult to enforce than composition of matter patents because, for example, of the risks that the FDA may approve alternative uses of the subject compounds not covered by the method of use, formulation or manufacturing method patents, and others may engage in off-label sale or use of the subject compounds. Physicians are permitted to prescribe an approved product for uses that are not described in the product's labeling. Although off-label prescriptions may infringe our method of use patents, the practice is common across medical specialties and such infringement is difficult to prevent or prosecute. FDA approval of uses of a generic version of tamibarotene or SY-2101 that are not covered by our patents would limit our ability to generate revenue from the sale of such product candidates, if approved for commercial sale. In addition, any off-label use of a generic version of tamibarotene would limit our ability to generate revenue from the sale of tamibarotene, if approved for commercial sale.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretations, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could harm our business, financial condition, results of operations and prospects.

We may not be successful in obtaining or maintaining necessary rights to current or future product candidates through acquisitions and in-licenses.

We currently have rights to certain intellectual property, through ownership or licenses from third parties, to develop and commercialize tamibarotene for human cancers in North and South America and Europe, Israel, Russia and Australia, and for SY-2101 and SY-5609 for all potential uses in North America and major markets in Europe and elsewhere. Because our programs may require the use of proprietary rights by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license from third parties any intellectual property rights directed to compositions, methods of use, or processes that we identify as necessary for any product candidates. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with non-profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us or we may decide not to execute such option if we believe such license is not necessary to pursue our program. If we are unable or opt not to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidate, which could harm our business significantly.

We depend upon our license with TMRC, and we may not be able to maintain that license.

We have entered into a standby license with TMRC and Toko Pharmaceuticals Ind. Co. Ltd., or Toko, providing that if at any time the license agreement between Toko and TMRC relating to the tamibarotene rights that TMRC has licensed to us terminates or otherwise ceases to be in effect for any reason, Toko will grant directly to us such rights and licenses with respect to tamibarotene as are necessary for us to continue to develop tamibarotene. If the TMRC license agreement terminates and this standby license terminates, then we may lose rights to tamibarotene that may be necessary to the development and commercialization of tamibarotene, which could have a material adverse impact on our business.

If we are unable to obtain and maintain sufficient patent protection for any product candidates, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our product candidates may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary product candidates. If we do not adequately protect our intellectual property, our competitors may be able to erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we file patent applications in the United States and abroad related to our novel product candidates that are important to our business. We also license or purchase patent applications filed by others. The patent application and approval processes are expensive and time consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner.

Agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented and may not be able to secure, maintain, or successfully enforce necessary or desirable patent protection from those patent rights. We have not had and do not have primary control over patent prosecution and maintenance for certain of the patents and patent applications we license, and therefore cannot guarantee that these patents and applications will be prosecuted in a manner consistent with the best interests of our business. We cannot be certain that patent prosecution and maintenance activities by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents.

We, or any partners, collaborators or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection for them. Therefore, we may miss potential opportunities to strengthen our patent position.

It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If we or our partners, collaborators, licensees, or licensors, whether current or future, fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our partners, collaborators, licensees or licensors, are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised. If there are material defects in the form, preparation, prosecution, or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain.

Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent except that, prior to March 16, 2013 in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases, not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly, we cannot be certain that parties from whom we do or may license or purchase patent rights were the first to make relevant claimed inventions, or were the first to file for patent protection for them. If third parties have filed patent applications on inventions claimed in our patents or applications on or before March 15, 2013, an interference proceeding in the United States can be initiated by such third parties to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. If third parties have filed such applications after March 15, 2013, a derivation proceeding in the United States can be initiated by such third parties to determine whether our invention was derived from theirs.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it may be used to invalidate a patent, or may prevent a patent from issuing from a pending patent application. For example, such patent filings may be subject to a third-party pre-issuance submission of prior art to the USPTO or to other patent offices around the world. Alternately or additionally, we may become involved in post-grant review procedures, oppositions, derivations, proceedings, reexaminations, *inter partes* review or interference proceedings, in the United States or elsewhere, challenging patents or patent applications in which we have rights, including patents on which we rely to protect our business. An adverse determination in any such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

Pending and future patent applications may not result in patents being issued which protect our business, in whole or in part, or which effectively prevent others from commercializing competitive products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States.

Issued patents that we have or may obtain or license may not provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to

circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

Pursuant to the terms of some of our license agreements with third parties, some of our third-party licensors have the right, but not the obligation, in certain circumstances to control enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents. Even if we are permitted to pursue such enforcement or defense, we will require the cooperation of our licensors, and cannot guarantee that we would receive it and on what terms. We cannot be certain that our licensors will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. If we cannot obtain patent protection, or enforce existing or future patents against third parties, our competitive position and our financial condition could suffer.

If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed.

In addition to the protection afforded by patents, we may also rely on trade secret protection. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, consultants, independent contractors, advisors, contract manufacturers, suppliers and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including any information we hold in confidence or as a trade secret, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated confidential information or a trade secret is difficult, expensive and time consuming, and the outcome is unpredictable. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. Further, if any of our confidential information or trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving one or more of our patents could limit our ability to assert those patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive

these results to be negative, it could adversely affect the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates without infringing the intellectual property and other proprietary rights of third parties. Third parties may have U.S. and non-U.S. issued patents and pending patent applications relating to compounds and methods of use for the treatment of the disease indications for which we are developing our product candidates. If any third-party patents or patent applications are found to cover our product candidates or their methods of use, we may not be free to manufacture or market our product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our product candidates, including interference proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us based on existing or future intellectual property rights. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. It is possible, however, that we would be unable to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. Alternatively, or additionally, it could include terms that impede or destroy our ability to compete successfully in the commercial marketplace. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Patent reform legislation in the United States, including the Leahy-Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011, and many of the substantive changes became effective on March 16, 2013. The America Invents Act reforms United States patent law in part by changing the U.S. patent system from a "first to invent" system to a "first inventor to file" system, expanding the definition of prior art, and developing a

post-grant review system. This legislation changes United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 16, 2013.

Further, the America Invents Act created new procedures to challenge the validity of issued patents in the United States, including post-grant review and *inter partes* review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent with an effective filing date of March 16, 2013 or later, a petition for post-grant review can be filed by a third party in a nine-month window from issuance of the patent. A petition for *inter partes* review can be filed immediately following the issuance of a patent if the patent has an effective filing date prior to March 16, 2013. A petition for *inter partes* review can be filed after the nine-month period for filing a post-grant review petition has expired for a patent with an effective filing date of March 16, 2013 or later. Post-grant review proceedings can be brought on any ground of invalidity, whereas *inter partes* review proceedings can only raise an invalidity challenge based on published prior art and patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts and use a lower burden of proof than used in litigation in U.S. federal courts. Therefore, it is generally considered easier for a competitor or third party to have a U.S. patent invalidated in a USPTO post-grant review or *inter partes* review proceeding than invalidated in a litigation in a U.S. federal court. If any of our patents are challenged by a third party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which would result in a loss of the challenged patent right to us.

In addition, the USPTO continues to modify its guidelines regarding subject matter eligibility, a process that began with decisions rendered in *Association for Molecular Pathology v. Myriad Genetics, Inc.*; *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*; and *Promega Corp. v. Life Technologies Corp.* Those court decisions have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We may not be able to enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products.

Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, including India, China and other countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop and market their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Further, a decree was adopted by the Russian government in March 2022 allowing Russian companies and individuals to exploit inventions owned by patent holders from the United States without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia.

Agreements through which we license patent rights may not give us sufficient rights to permit us to pursue enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents (or control of enforcement or defense) of such patent rights in all relevant jurisdictions as requirements may vary.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Moreover, such proceedings could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

Patent terms may be inadequate to protect our competitive position on our products for an adequate amount of time.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). The applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree, however, with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property or claiming ownership of what we regard as our own intellectual property.

Many of our employees and our licensors' employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, some of which may be competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants, contractors and vendors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the

patent application process and after a patent has issued. There are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction.

Risks Related to Regulatory Approval and Marketing of Our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time consuming and uncertain and may prevent us or any collaborators from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any collaborators, will obtain marketing approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We, and any collaborators, are not permitted to market our product candidates in the United States or in other countries until we, or they, receive approval of an NDA from the FDA or marketing approval from applicable regulatory authorities outside the United States. Our product candidates are in various stages of development and are subject to the risks of failure inherent in drug development. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals, including FDA approval of an NDA.

The process of obtaining marketing approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. The FDA or other regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Moreover, the FDA or other regulatory authorities may fail to approve the companion diagnostics we contemplate developing with partners. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we, or any collaborators, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Any delay in obtaining or failure to obtain required approvals could negatively affect our ability or that of any collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

If we are required by the FDA to obtain clearance or approval of a companion diagnostic in connection with approval of a candidate therapeutic product, and we do not obtain or there are delays in obtaining FDA clearance or approval of a diagnostic device, we will not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and *in vitro* companion diagnostics. According to the guidance, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared for that indication. Under the Federal Food, Drug, and Cosmetic Act, or FDCA, companion diagnostics are regulated as medical devices and the FDA has generally required companion diagnostics intended to select the patients who will respond to cancer treatment to obtain premarket approval, or a PMA. Consequently, we anticipate that certain of our companion diagnostics may require us or our collaborators to obtain a PMA. For example, we expect that the FDA will require a PMA for the companion diagnostic being developed by Qiagen for use with tamibarotene to identify genomically defined subsets of patients with AML or MDS using our *RARA* biomarker.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, involves a rigorous premarket review during which the sponsor must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA approval is not guaranteed and may take considerable time, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. As a result, if we or our collaborators are required by the FDA to obtain approval of a companion diagnostic for a candidate therapeutic product, and we or our collaborators do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we may not be able to effectively commercialize the product candidate and our ability to generate revenue will be materially impaired.

In its August 2014 guidance, the FDA also indicated that companion diagnostics used to make treatment decisions in clinical trials of a therapeutic product generally will be considered investigational devices. When a companion diagnostic is used to make critical treatment decisions, such as patient selection, the FDA stated that the diagnostic will be considered a significant risk device requiring an investigational device exemption. The FDA may find that a companion diagnostic that we, alone or with a third party such as Qiagen, plan to develop does not comply with those requirements and, if this were to occur, we would not be able to proceed with our planned trial of the applicable product candidate in these patient populations.

We believe that adoption of screening and treatment into clinical practice guidelines is important for payer access, reimbursement, utilization in medical practice and commercial success, but both our collaborators and we may have difficulty gaining acceptance of the companion diagnostic into clinical practice guidelines. If such companion diagnostics fail to gain market acceptance, it would have an adverse effect on our ability to derive revenues from sales, if any, of any of our product candidates that are approved for commercial sale. In addition, any companion diagnostic collaborator or third party with whom we contract may decide not to commercialize or to discontinue selling or manufacturing the companion diagnostic that we anticipate using in connection with development and commercialization of our product candidates, or our relationship with such collaborator or third party may otherwise terminate. We may not be able to enter into arrangements with another provider to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our product candidates.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad. Any approval we are granted for our product candidates in the United States would not assure approval of our product candidates in foreign jurisdictions.

In order to market and sell our products in the European Union and other foreign jurisdictions, we, and any collaborators, must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We, and any collaborators, may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may file for marketing approvals but not receive necessary approvals to commercialize our products in any market.

In many countries outside the United States, a product candidate must also be approved for reimbursement before it can be sold in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. Obtaining non-U.S. regulatory approvals and compliance with non-U.S. regulatory requirements could result in significant delays, difficulties and costs for us and any collaborators and could delay or prevent the introduction of our product candidates in certain countries. In addition, if we or any collaborators fail to obtain the non-U.S. approvals required to market our product candidates outside the United States or if we or any collaborators fail to comply with applicable non-U.S. regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects may be adversely affected.

Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the recent withdrawal of the United Kingdom from the European Union, commonly referred to as Brexit. Effective January 1, 2021, the United Kingdom is no longer part of the European Single Market and European Union Customs Union. As of January 1, 2021, the Medicines and Healthcare Products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland will continue to be subject to European Union rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has been incorporated into the domestic law of the body of European Union law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the European Union.

Since a significant proportion of the regulatory framework for pharmaceutical products in the U.K. covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit may have a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the U.K. For example, the U.K. is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in the U.K. Until December 31, 2023, it is possible for the MHRA to rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom for our product candidates, which could significantly and materially harm our business.

We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets (such as the ongoing conflict between Ukraine and Russia); compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the United States.

We, or any collaborators, may not be able to obtain orphan drug designation or orphan drug exclusivity for our product candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving competing products.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States. Generally, a product with orphan drug designation only becomes entitled to orphan drug exclusivity if it receives the first marketing approval for the indication for which it has such designation, in which case the FDA or the EMA will be precluded from approving another marketing application for the same product for that indication for the applicable exclusivity period. The applicable exclusivity period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified.

We have obtained orphan drug designation for tamibarotene for the treatment of MDS in the United States, and for the treatment of AML in the United States and in Europe. In addition, the EMA has issued a positive opinion on our application for orphan drug designation for tamibarotene for the treatment of MDS in Europe. SY-2101 has also received orphan drug designation for the treatment of APL in the United States and for the treatment of AML in Europe, and SY-5609 has received orphan drug designation for the treatment of pancreatic cancer in the United States. In the future, we or any collaborators may seek orphan drug designations for tamibarotene, SY-2101 or SY-5609 in other indications or territories or for other product candidates and may be unable to obtain such designations. Even if we do secure such designations and orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Further, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, to be more effective or to make a major contribution to patient care. Finally, orphan drug exclusivity may be lost if the FDA or the EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term “same disease or condition” means the designated “rare disease or condition” and could not be interpreted by the Agency to mean the “indication or use.” Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of the court’s order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

Any product candidate for which we or our collaborators obtain marketing approval is subject to ongoing regulation and could be subject to restrictions or withdrawal from the market, and we may be subject to substantial penalties if we fail to comply with regulatory requirements, when and if any of our product candidates are approved.

Any product candidate for which we or our collaborators obtain marketing approval will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. In addition, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy. Accordingly, if we receive marketing approval for one or more of our product candidates, we would continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we fail to comply with these requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any products could be limited, which could adversely affect our ability to achieve or sustain profitability.

We and our collaborators must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription products are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product’s approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. In September 2021, the FDA published final regulations which describe the types of evidence that the FDA will consider in determining the intended use of a drug or biologic. Moreover, with passage of the Pre-Approval Information Exchange Act, or PIE Act, in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Nonetheless, the FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. Violations of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

Failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on distribution or use of a product;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;

- recall of products;
- damage to relationships with collaborators;
- unfavorable press coverage and damage to our reputation;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions or the imposition of civil or criminal penalties; and
- litigation involving patients using our products.

Non-compliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the EU's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

We may seek certain designations for our product candidates, including Breakthrough Therapy and Fast Track designations, but we might not receive such designations, and even if we do, such designations may not lead to a faster development or regulatory review or approval process.

We may seek certain designations for one or more of our product candidates that could expedite review and approval by the FDA. A Breakthrough Therapy product is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For products that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Products designated as Breakthrough Therapies by the FDA may also be eligible for priority review if supported by clinical data at the time the NDA is submitted to the FDA.

The FDA may also designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For example, the FDA has granted Fast Track designation to tamibarotene for the treatment of HR-MDS. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees.

Designation as a Breakthrough Therapy or Fast Track is within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for these designations, the FDA may disagree and instead determine not to make such designation. Further, even though we have received Fast Track designation for tamibarotene for the treatment of HR-MDS, and even if we receive Breakthrough Therapy or Fast Track designation for one or more of our other product candidates, the receipt of such designations may not result in a faster development or regulatory review or approval process compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, the FDA may later decide that tamibarotene or one or more of our other product candidates no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Inadequate funding for the FDA, the SEC and other government agencies, including from government shut downs, or other disruptions to these agencies' operations, could hinder their ability to hire and retain key leadership and other

personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Separately, in response to the COVID-19 pandemic in 2020 and 2021, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. As of May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the ongoing COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to continue its current pace and review timelines could be extended; therefore, the FDA may be unable to complete such required inspections during the review period. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities.

Current and future legislation may result in more rigorous coverage and reimbursement criteria for product candidates, which could increase the difficulty and cost for us and any collaborators to obtain marketing approval of our product candidates.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other

healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the ACA, there have been and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act, or TCJA, in 2017, Congress repealed the “individual mandate.” The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseparable feature of the ACA and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the ACA. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans’ access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

The TCJA, as amended by the CARES Act, additionally contains changes in tax law that could adversely affect our business or financial condition. The TCJA contains significant changes to corporate taxation, including a reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), the limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely and such net operating losses arising in taxable years beginning before January 1, 2021 are generally eligible to be carried back up to five years), one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, the elimination of U.S. tax on foreign earnings (subject to certain important exceptions), the allowance of immediate deductions for certain new investments instead of deductions for depreciation expense over time, and the modification or repeal of many business deductions and credits. In addition to the CARES Act, as part of Congress’ response to the COVID-19 pandemic, economic relief legislation has been enacted in 2020 and 2021 containing tax provisions. Regulatory guidance under the TCJA and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen the impact of these laws on our business and financial condition. Also, as a result of the changes in the U.S. presidential administration and control of the U.S. Senate, additional tax legislation may be enacted; any such additional legislation could have an impact on us.

Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope or amount, our business could be materially harmed.

Current and future legislation designed to reduce prescription drug costs may affect the prices we and any collaborators may obtain for our product candidates.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. The implementation of the rule was delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation, and was subsequently delayed until January 1, 2026 by the Infrastructure Investment and Jobs Act.

More recently, on August 16, 2022, the IRA was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years.

Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated \$4,000 a year in 2024 and, thereafter beginning in 2025, at \$2,000 a year.

At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Finally, outside the United States, in some nations, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we, or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

We may be subject to certain healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, fines, disgorgement, exclusion from participation in government healthcare programs, curtailment or restricting of our operations, and diminished profits and future earnings.

Healthcare providers, third-party payors and others will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with healthcare providers and third-party payors will expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Potentially applicable U.S. federal and state healthcare laws and regulations include the following:

Anti-Kickback Statute. The federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid;

False Claims Laws. The federal false claims laws, including the civil False Claims Act, impose criminal and civil penalties, including those from civil whistleblower or *qui tam* actions against individuals or entities for knowingly presenting, or causing to be presented to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

HIPAA. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing or attempting to execute a scheme to defraud any healthcare benefit program;

HIPAA and HITECH. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or the HITECH Act, also imposes obligations on certain types of individuals and entities, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. While these provisions likely will not apply to us directly, they will apply to many of our partners and other entities assisting with our clinical trials and future activities, and therefore may impact our relationships with these entities and related costs;

False Statements Statute. The federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

Transparency Requirements. The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value, including ownership and investment interests, to physicians and their family members; and

Analogous State and Foreign Laws. Analogous state laws and regulations, such as state anti-kickback and false claims laws, and transparency laws, may apply to sales or marketing arrangements, and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures. Many state laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. Foreign laws also govern the privacy and security of health information in many circumstances.

Efforts to ensure that our business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, and reputational harm, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the U.S., EU and United Kingdom. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects.

There are numerous U.S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future.

If we are unable to properly protect the privacy and security of protected health information, we could be found to have breached our contracts. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our

ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems.

In 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation, or the GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah, and Connecticut already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three states will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Similar to the laws in the U.S., there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area, or the EEA, and the processing of personal data that takes place in the EEA, is regulated by the GDPR, which went into effect in May 2018 and which imposes obligations on companies that operate in our industry with respect to the processing of personal data and the cross-border transfer of such data. The GDPR imposes onerous accountability obligations requiring data controllers and processors to maintain a record of their data processing and policies. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

The GDPR places restrictions on the cross-border transfer of personal data from the EU to countries that have not been found by the EC to offer adequate data protection legislation, such as the U.S. There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U.S. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the U.S. While we were not self-certified under the Privacy Shield, this CJEU decision may lead to increased scrutiny on data transfers from the EEA to the U.S. generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

Additionally, in October 2022, President Joe Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-US Privacy Shield. The EC initiated the process to adopt an adequacy decision for the EU-US Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

Following the withdrawal of the U.K. from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the UK and includes parallel obligations to those set forth by GDPR. In relation to data transfers, both the U.K. and the EU have determined, through separate "adequacy" decisions, that data transfers between the two jurisdictions are in compliance with the U.K. Data Protection Act and the GDPR, respectively. Any changes or updates to these adequacy decisions have the potential to impact our business.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and the sale and distribution of commercial products, through increased compliance costs, costs associated with contracting and potential enforcement actions.

While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non-compliant. Similarly, failure to comply with federal and state laws in the U.S. regarding privacy and security of personal information could expose us to penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government-imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business, financial condition, results of operations or prospects.

We are subject to U.S. and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

We have adopted a Code of Business Conduct and Ethics that mandates compliance with the FCPA and other anti-corruption laws applicable to our business throughout the world. We cannot assure you, however, that our employees and third-party intermediaries will comply with this code or such anti-corruption laws. Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

We are subject to governmental export and import controls that could impair our ability to compete in international markets due to licensing requirements and subject us to liability if we are not in compliance with applicable laws.

Our products and solutions are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, and various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls. Exports of our products and solutions outside of the United States must be made in compliance with these laws and regulations. If we fail to comply with these laws and regulations, we and certain of our employees could be subject to substantial civil or criminal penalties, including the possible

loss of export or import privileges; fines, which may be imposed on us and responsible employees or managers; and, in extreme cases, the incarceration of responsible employees or managers.

In addition, changes in our products or solutions or changes in applicable export or import laws and regulations may create delays in the introduction, provision, or sale of our products and solutions in international markets, prevent customers from using our products and solutions or, in some cases, prevent the export or import of our products and solutions to certain countries, governments or persons altogether. Any limitation on our ability to export, provide, or sell our products and solutions could adversely affect our business, financial condition and results of operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, but this insurance may not provide adequate coverage against potential liabilities. We do not, however, maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development or production efforts. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The most recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets, and it is unclear what impact the decision by the United Kingdom to leave the European Union will have on the global economy. A severe or prolonged economic downturn, such as the most recent global financial crisis, could result in a variety of risks to our business, including weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Our internal computer systems, or those of any collaborators or contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures and certain data recovery measures, our internal computer systems and those of our current and any collaborators and other contractors or consultants are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, sabotage, natural disasters, terrorism, war and telecommunication and electrical failures. We have experienced, and may experience in the future, security breaches of our information technology systems. Any system failure, accident or security breach that causes interruptions in our operations, for us or those third parties with which we contract, could result in a material disruption of our product development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from an ongoing, completed or future clinical trial could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we may incur liabilities, our competitive position could be harmed and the further development and commercialization of our product candidates may

be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees. In addition, outside parties have attempted, and may in the future attempt, to penetrate our systems or those of our vendors or fraudulently induce our employees or employees of our vendors to disclose sensitive information to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and viruses, and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed, we could lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely.

Our employees, independent contractors, CROs, consultants, commercial partners, vendors, and principal investigators may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, CROs, consultants, commercial partners, vendors and principal investigators, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Risks Related to Our Business Operations, Employee Matters and Managing Growth

Public health epidemics or outbreaks, including COVID-19, have had, and may continue to have, an adverse impact on our business.

Public health crises such as pandemics, epidemics and outbreaks could adversely impact our business. For example, COVID-19 has impacted, and it or another public health epidemic or outbreak may impact in the future, our operations and those of our third-party partners. The ultimate impact of any such public health epidemic or outbreak will depend on future developments which are highly uncertain and cannot be predicted with confidence, including the scope, severity, duration and any recurrence of such pandemic, actions taken to contain the pandemic or mitigate its impact, the direct and indirect economic effects of the pandemic and containment measures, the effectiveness of vaccination and booster vaccination campaigns, work from home and return-to-work arrangements, compliance with governmental measures in connection with such pandemic, among others. Such pandemic or a similar public health epidemic or outbreak could adversely impact our ability to conduct clinical trials and our business generally and could have a material adverse impact on our operations and financial condition and results. In addition, a recession, depression or other sustained adverse market event resulting from the COVID-19 pandemic or a similar public health epidemic or outbreak could materially and adversely affect our business and the value of our common stock.

Our future success depends on our ability to attract and retain key management and scientists, development, medical and commercial staff, consultants and advisors.

Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on the pharmaceutical research and development and business development expertise of Nancy Simonian, M.D., our president and chief executive officer;

Conley Chee, our chief commercial officer; Jason Haas, our chief financial officer; Eric R. Olson, Ph.D., our chief scientific officer; Gerald E. Quirk, Esq., our chief legal officer; David A. Roth, M.D., our chief medical officer; and Kristin Stephens, our chief development officer. Each member of our management team is employed "at will," meaning any of them may terminate his or her employment with us at any time with or without notice and for any reason or no reason. We also rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy.

Our industry has experienced a high rate of turnover of management, scientific, clinical, medical and commercial personnel in recent years. If we lose one or more of our executive officers or other key employees, our ability to implement our business strategy successfully could be seriously harmed. Replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain marketing approval of and commercialize products successfully. We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to attract and reward qualified individuals than we do. In addition, due to the risks associated with developing a new class of medicine, we may face additional challenges in attracting and retaining employees. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize our product candidates will be limited.

We expect to expand our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, drug manufacturing, regulatory affairs and sales, marketing and distribution. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Our management may need to devote a significant amount of its attention to managing these growth activities. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion or relocation of our operations, retain key employees, or identify, recruit and train additional qualified personnel. Our inability to manage the expansion or relocation of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of our product candidates.

We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.

In the future, we may enter into transactions to acquire other businesses, products or technologies. Because we have not made any acquisitions to date, our ability to do so successfully is unproven. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non-disruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

Our operations or those of the third parties upon whom we depend might be affected by the occurrence of a catastrophic event, such as a terrorist attack, war or other armed conflict, geopolitical tensions or trade wars, pandemic or natural disaster.

We depend on our employees, consultants, CROs, as well as regulatory agencies and other parties, for the continued operation of our business. Despite any precautions that we or any third parties on whom we depend take for catastrophic

events, including terrorist attacks, wars or other armed conflicts, geopolitical tensions or trade wars, pandemics or natural disasters, these events could result in significant disruptions to our research and development, manufacturing, preclinical studies, clinical trials, and, ultimately, if approved, the commercialization of our products. Long-term disruptions in the infrastructure caused by these types of events, such as natural disasters, which are increasing in frequency due to the impacts of climate change, the outbreak of wars or other armed conflicts, the escalation of hostilities, geopolitical tensions or trade wars, acts of terrorism or “acts of God,” particularly involving geographies in which we or third parties on whom we depend have offices, manufacturing or clinical trial sites, could adversely affect our businesses. We cannot be certain what the overall impact of such events will be on our business or on the business of any third parties on whom we depend. Although we carry business interruption insurance policies and typically have provisions in our contracts that protect us in certain events, our coverage might not include or be adequate to compensate us for all losses that may occur. Any catastrophic event affecting us, our CROs, regulatory agencies or other parties with which we are engaged could have a material adverse effect on our operations and financial performance.

Risks Related to Our Common Stock

The price of our common stock is likely to be highly volatile, which could result in substantial losses for our stockholders.

Our stock price is likely to be highly volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may lose some or all of your investment. The market price for our common stock may be influenced by many factors, including:

- the timing and results of clinical trials of tamibarotene, SY-2101 and SY-5609;
- the success of existing or new competitive products or technologies;
- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- commencement or termination of collaborations for our research or development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results or development timelines or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;

- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions;
- actual or threatened public health emergencies and outbreaks of disease (including, for example, the COVID-19 pandemic); and
- the other factors described in this “Risk Factors” section and elsewhere in this Annual Report.

In the past, companies that have experienced volatility in the market price of their stock have been subject to an increased incidence of securities class action litigation. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and resources, which could harm our business. We may also face other material adverse consequences due to volatility or a sustained decrease in the price of our common stock, such as negative publicity, a decreased ability to obtain additional financing, diminished investor and/or employee confidence, and the loss of business development opportunities, some or all of which may contribute to a further decline in our stock price.

We must maintain effective internal control over financial reporting, and if we are unable to do so, the accuracy and timeliness of our financial reporting may be adversely affected, which could have a material adverse effect on our business and stock price.

We must maintain effective internal control over financial reporting in order to accurately and timely report our results of operations and financial condition. In addition, as a public company, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, requires, among other things, that we assess the effectiveness of our disclosure controls and procedures quarterly and the effectiveness of our internal control over financial reporting at the end of each fiscal year.

The rules governing the standards that must be met for our management to assess our internal control over financial reporting pursuant to Section 404 of the Sarbanes-Oxley Act are complex and require significant documentation, testing and possible remediation. These standards require that our audit committee be advised and regularly updated on management’s review of internal control over financial reporting. Our management may not be able to effectively and timely implement controls and procedures that comply with the increased regulatory compliance and reporting requirements that are applicable to us as a public company. If we fail to staff our accounting and finance function adequately or maintain internal control over financial reporting adequate to meet the demands that are placed upon us as a public company, including the requirements of the Sarbanes-Oxley Act, our business and reputation may be harmed and our stock price may decline.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2022, we had federal and state net operating loss carryforwards of \$300.2 million and \$300.2 million, respectively, and federal and state research and development tax credit carryforwards of \$1.9 million and \$0.5 million, respectively. These carryforwards could expire unused and be unavailable to offset future income tax liabilities. Our net operating loss carryforwards generated before 2018 will generally expire at various dates through 2037 and our research and development tax credit carryforwards will generally expire at various dates through 2042.

The TCJA, as amended by the CARES Act, contains significant changes with respect to federal net operating loss carryforwards, including the limitation of the deduction for net operating loss carryforwards to 80% of current year taxable income and the elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely and such net operating losses arising in taxable years beginning before January 1, 2021 are generally eligible to be carried back up to five years). Regulatory guidance under the TCJA and the CARES Act is and continues to be forthcoming, and such guidance could further impact our ability to utilize our net operating loss carryforwards.

In addition, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Furthermore, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an “ownership change,” which is generally defined as a cumulative change in ownership of significant shareholders of greater than 50%, by value, over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards and research and development tax credit carryforwards to offset its post-change income may be limited. Our acquisition of Tyme Technologies, Inc. and concurrent private financing in September 2022 resulted in an ownership change for purposes of

Section 382, and as a result our ability to use our historical net operating loss and tax credit carryforwards will be materially limited. Such limitation, or any adjustments to our carryforwards made by the Internal Revenue Service or state tax authorities, could harm our future operating results by effectively increasing our future tax obligations.

We do not anticipate paying any cash dividends on our capital stock in the foreseeable future. Accordingly, stockholders must rely on capital appreciation, if any, for any return on their investment.

We have never declared nor paid cash dividends on our capital stock. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our business. In addition, the terms of our term loan facility with Oxford precludes us from paying cash dividends to our stockholders without Oxford's consent. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Concentration of ownership of our common stock among our principal stockholders may prevent new investors from influencing significant corporate decisions.

Our stockholders who own more than 5% of our outstanding common stock and their affiliates, in the aggregate, beneficially own a significant portion of our common stock. As a result, if these stockholders were to choose to act together, they would be able to substantially influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would substantially influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management or the board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Provisions in our certificate of incorporation and bylaws and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us.

Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that all members of the board are not elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on at stockholder meetings;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call a special meeting of stockholders;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and

- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our certificate of incorporation or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders. This could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock will likely depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us, or provide favorable coverage. Securities or industry analysts may elect not to provide research coverage of our common stock, and such lack of research coverage may negatively impact the market price of our common stock. In the event we do have analyst coverage, if one or more analysts downgrade our stock or change their opinion of our stock, our share price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not Applicable.

ITEM 2. PROPERTIES

We currently occupy approximately 52,859 rentable square feet of office and laboratory space in Cambridge, Massachusetts under a lease that expires in February 2030. We have an option to extend the lease term for 10 additional years. We believe that our office and laboratory space is sufficient to meet our current needs and that suitable additional space will be available as and when needed.

ITEM 3. LEGAL PROCEEDINGS

None.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT’S COMMON EQUITY, RELATED STOCKHOLDER MATTERS, AND ISSUER PURCHASES OF EQUITY SECURITIES

Certain Information Regarding the Trading of Our Common Stock

Our common stock trades under the symbol “SYRS” on the Nasdaq Global Select Market and has been publicly traded since June 30, 2016. Prior to this time, there was no public market for our common stock.

Holders of Our Common Stock

As of February 27, 2023, there were approximately 76 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in “nominee” or “street” name.

ITEM 6. RESERVED

Not applicable.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our audited financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K, or Annual Report. Some of the information contained in this discussion and analysis and set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in Part I, Item 1A of this Annual Report for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company committed to developing new standards of care for the frontline treatment of patients with hematologic malignancies. Driven by the motivation to help patients with blood disorders that have largely eluded other targeted approaches, we are advancing a late-stage clinical pipeline which includes our lead product candidates:

- Tamibarotene, a selective retinoic acid receptor alpha, or RAR α , agonist for which we are conducting SELECT-MDS-1, a Phase 3 clinical trial evaluating tamibarotene in combination with azacitidine in a genomically defined subset of patients with higher-risk myelodysplastic syndrome, or HR-MDS, and for which we are conducting SELECT-AML-1, a randomized Phase 2 clinical trial evaluating tamibarotene in combination with venetoclax and azacitidine in a genomically defined subset of newly diagnosed patients with acute myeloid leukemia, or AML, who are not suitable candidates for standard intensive chemotherapy; and
- SY-2101, a novel oral form of arsenic trioxide, or ATO, which we are evaluating in a dose confirmation study in patients with newly diagnosed low-risk acute promyelocytic leukemia, or APL.

In addition, we are evaluating SY-5609, a highly selective and potent oral inhibitor of cyclin-dependent kinase 7, or CDK7, as a single agent in patients with select solid tumors and in combination with chemotherapy in pancreatic cancer patients in a Phase 1 clinical trial. SY-5609 is also being evaluated in combination with atezolizumab, a PD-L1 inhibitor, in BRAF-mutant colorectal cancer in an arm of a Phase 1/1b clinical trial sponsored by F. Hoffmann-La Roche AG, or Roche, which is actively enrolling. We also have multiple preclinical and discovery programs in oncology, including SY-12882, our oral CDK12 inhibitor, and programs targeting the inhibition of CDK11 and WRN. We are currently exploring partnership opportunities for SY-5609 and for our oncology discovery programs. We have also entered into a collaboration with Global Blood Therapeutics, Inc., now a subsidiary of Pfizer Inc., or GBT, to discover, develop and commercialize novel therapies for sickle cell disease and beta thalassemia.

Tamibarotene

At the 62nd American Society of Hematology Annual Meeting and Exposition held in December 2020, or ASH 2020, we presented data from our fully enrolled Phase 2 clinical trial assessing the safety and efficacy of tamibarotene in combination with azacitidine in newly diagnosed AML patients who are not suitable candidates for standard intensive chemotherapy, as well as in relapsed or refractory, or R/R, AML patients who have been prospectively selected using our proprietary *RARA*, the gene that codes for RAR α , biomarker. As of an October 1, 2020 data cut-off, 51 newly diagnosed unfit AML patients, including patients with and without *RARA* gene overexpression, were eligible for a safety analysis. Among these patients, tamibarotene in combination with azacitidine was generally well-tolerated, with no evidence of increased toxicity relative to either as a single agent, including rates of myelosuppression that were comparable to single agent azacitidine. As of the data cut-off, of the 18 patients with *RARA* overexpression that were evaluable for clinical response, the composite complete response rate was 61%, with 50% of patients achieving complete response, or CR, and 11% achieving a complete response with incomplete blood count recovery, or CRi. The median time to initial composite CR was 1.2 months, the median duration of composite complete remission was 10.8 months, and the median overall survival, or OS, among patients who achieved a CR or CRi was 18.0 months. As of the data cut-off, of the 28 patients without *RARA* overexpression that were evaluable for clinical response, the overall response rate, or ORR, was 43%, with a composite complete response rate of 32%, with 25% of patients achieving CR and 7% achieving CRi. The median time to initial composite complete remission was 3.0 months, and the median duration of composite complete remission was 10.3 months. We also presented translational data demonstrating that most newly diagnosed unfit AML patients with *RARA* overexpression enrolled in our Phase 2 study had a monocytic disease phenotype that is associated with resistance to venetoclax. These data suggest that the *RARA* biomarker not only selects for patients who are more likely to respond to treatment with tamibarotene but also for patients who may be less likely to benefit from treatment with venetoclax. Approximately 25,000 patients are diagnosed with unfit AML in the United States and Europe annually and we expect the overall total addressable market opportunity for all AML patients to grow to approximately \$6.6 billion by 2025.

Based on these data and our assessment of ongoing areas of high unmet need, we advanced tamibarotene in combination with azacitidine into a registration-enabling Phase 3 clinical trial in newly diagnosed HR-MDS patients with *RARA* overexpression, which we refer to as SELECT-MDS-1. HR-MDS is a hematologic malignancy that is closely related to AML, and we believe that approximately 50% of HR-MDS patients overexpress *RARA*. We believe that approximately 21,000 patients are diagnosed with HR-MDS in the United States and Europe annually and we expect the total addressable market opportunity for MDS patients of all risk groups to grow to approximately \$3.3 billion by 2026. We plan to enroll approximately 190 newly diagnosed HR-MDS patients with *RARA* overexpression in the double-blind placebo-controlled trial, randomized 2:1 to receive tamibarotene in combination with azacitidine or placebo with azacitidine, respectively. In recent communications, the FDA has continued to support the use of the CR rate as an acceptable efficacy endpoint for regulatory decision-making for treatments of newly diagnosed higher-risk MDS with supporting data on durability of remission. The trial is designed with 90% power and a one-sided alpha of 0.025 to detect a difference in CR rates between the experimental and control arms. We are currently dosing patients in SELECT-MDS-1, and we expect to complete enrollment in the fourth quarter of 2023 and report data from the SELECT-MDS-1 trial in the third quarter of 2024.

In addition, we advanced tamibarotene in combination with venetoclax and azacitidine in newly diagnosed unfit AML patients with *RARA* overexpression. Our ongoing Phase 2 clinical trial, known as SELECT-AML-1, included a single-arm safety lead-in to confirm the dosing regimen of the triplet to be used in the randomized portion of the trial, which will evaluate the safety and efficacy of tamibarotene in combination with venetoclax and azacitidine compared to venetoclax and azacitidine in approximately 80 patients randomized 1:1. We reported clinical activity data from the safety lead-in portion of the ongoing trial at the 64th Annual Meeting of the American Society of Hematology in December 2022, or ASH 2022. As of the data cut-off, eight newly diagnosed, unfit patients who were positive for *RARA* overexpression had been enrolled in the trial, including six who were evaluable for response. In this population, tamibarotene in combination with venetoclax and azacitidine administered at approved doses showed no evidence of increased toxicity relative to the doublet combination of venetoclax and azacitidine. This includes rates of myelosuppression, which were comparable to reports with venetoclax and azacitidine in this population. Among these patients, the CR/CRi rate was 83%, consisting of two patients (33%) who achieved a CR and three patients (50%) who achieved a CRi. Four of five patients (80%) who achieved a CR or CRi had a high monocytic expression score, or MES, which may be associated with venetoclax resistance. The median time to CR/CRi response was 33 days, the median duration of treatment was 76.5 days, and the median duration of follow-up was 107 days. These early data compare favorably to the standard-of-care combination of venetoclax and azacitidine, which shows composite CR rates of 66% in newly diagnosed unfit AML patients. The primary endpoint of the trial will be the composite CR rate. The trial will also evaluate the triplet as a salvage strategy for patients in the control arm who do not respond to venetoclax and azacitidine. We initiated the randomized portion of the trial in the first quarter of 2023, and we expect to report initial randomized data in the fourth quarter of 2023 and additional data in 2024.

In March 2022, we entered into an agreement with Qiagen Manchester Limited, or Qiagen, under which Qiagen agreed to develop and commercialize an assay as a companion diagnostic test to determine the expression level of our proprietary *RARA* biomarker for use with tamibarotene in newly diagnosed higher-risk MDS patients. Qiagen will also be responsible for obtaining and maintaining regulatory approvals for the commercial diagnostic test.

SY-2101

In December 2020, we acquired from Orsenix, LLC, or Orsenix, a novel oral form of ATO, which we refer to as SY-2101. SY-2101 is in development for the treatment of APL, a subtype of AML defined by a fusion of the *RARA* and promyelocytic leukemia, or *PML*, genes. APL represents approximately 10% of all AML cases, and approximately 2,000 patients are diagnosed with APL in the United States and Europe annually. An intravenously administered, or IV, formulation of ATO is approved for use in combination with All-Trans-Retinoic-Acid, or ATRA, in patients with newly diagnosed low-risk APL and, while curative in more than 80% of patients, its administration requires up to 140 two- to four-hour infusions over the typical course of induction and consolidation treatment. We believe SY-2101 has the potential to become the standard-of-care frontline therapy for APL by providing a substantially more convenient option that reduces the treatment burden on patients, improving access, and lowering costs to the healthcare system. In a prior Phase 1 clinical trial, SY-2101 demonstrated bioavailability, pharmacokinetic, or PK, exposures similar to IV ATO, and a generally well-tolerated safety profile. We are dosing patients in a dose confirmation study of SY-2101. The ongoing dose confirmation study is designed to evaluate the PK, food effect, safety and tolerability of SY-2101 and is expected to enroll between six and 24 adult APL patients undergoing consolidation with IV ATO plus ATRA. Participants receive a single dose of 15 mg of SY-2101 in both the fasted and in the fed state, and a single dose of IV ATO for PK assessments, with flexibility to allow for other SY-2101 doses to be evaluated. Daily administration of SY-2101 is also being evaluated in a multiple-dose treatment module substituting for IV ATO during consolidation to assess steady state SY-2101 PK and safety. Based on preliminary data

available to date in our ongoing Phase 1 dose confirmation study, SY-2101 administered at 15 mg achieved comparable PK (AUC and Cmax) exposures to IV ATO at the approved dose of 0.15 mg/kg. Additionally, based on the data available to date, SY-2101 showed high oral bioavailability of approximately 80% and continues to support a favorable tolerability profile.

To date, feedback from the United States Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, in the context of the original SY-2101 PK data supports a single registration-enabling study of approximately 215 patients with newly diagnosed low-risk APL, randomized 2:1 to receive SY-2101 or IV ATO and designed with molecular complete response and event-free survival as primary endpoints for potential approval. Based on the emerging PK cross-over data directly comparing SY-2101 to the approved dose of IV ATO in our dose confirmation trial, and assuming that additional data is supportive, we believe there may be an opportunity to explore a more efficient registration pathway to potential approval. We plan to provide an update on the dose confirmation study, as well as the development path and timing for further evaluation of SY-2101 in a registration enabling study in APL, in the second half of 2023.

SY-5609

At the European Society for Medical Oncology Congress held in September 2021, or ESMO 2021, we presented data from the dose-escalation portion of the Phase 1 multi-center, open-label study of SY-5609 evaluating patients with advanced breast, colorectal, lung, ovarian and pancreatic cancers, as well as patients with solid tumors of any histology harboring Rb pathway alterations. Patients were treated in cohorts exploring continuous daily dosing as well as intermittent dosing regimens, including seven days on treatment and seven days off, or 7d on/7d off, and five days on treatment and two days off, or 5d on/2d off. As of a July 6, 2021 data cut-off, 54 patients treated with single-agent SY-5609 in the study were eligible for a safety analysis and 45 patients were evaluable for clinical response. The median age of patients enrolled in the study was 65.5. Patients had been heavily pre-treated with as many as eight prior therapies and a median of four prior therapies. Across all doses and schedules, the majority of adverse events, or AEs, were low-grade and reversible, and there was a low rate of discontinuations due to AEs. The most common treatment-emergent AEs were gastrointestinal (nausea, diarrhea, decreased appetite, abdominal pain, vomiting), fatigue, thrombocytopenia, and anemia. Tolerability was optimized with the 7d on/7d off schedule, which had the lowest rates of treatment-emergent AEs relative to other regimens, while demonstrating comparable rates of stable disease, or SD, as seen with more dose-intense regimens, supporting the selection of this schedule for further development of SY-5609. The maximum tolerated dose of the 7d on/7d off schedule has not yet been reached as of the data cut-off date. Changes in POLR2A mRNA expression, a pharmacodynamic marker for CDK7 inhibition, were associated with anti-tumor activity and were sustained for at least three days following drug cessation, supporting intermittent dosing. As of the data cut-off date, thirteen response-evaluable patients (29%) had achieved SD, with tumor regressions of up to 20% in six of those patients, across multiple tumor types. The most substantial clinical activity was observed in heavily pre-treated patients with advanced pancreatic cancer, for which five of 13 (39%) evaluable patients achieved SD, with tumor reductions in two of those SD patients. Further, reductions in the CA 19-9 tumor marker, which is used in clinical practice to monitor tumor progression, were observed in three of four pancreatic cancer patients with serial CA 19-9 data, with these reductions ranging from 32% to 72%. Notably, one metastatic pancreatic cancer patient who had failed two prior lines of therapy and relapsed after a third line of treatment experienced prolonged SD of up to ten months. The analysis of clinical activity by tumor type and mutational status supported the mechanistic rationale for SY-5609 in Rb-altered and KRAS-mutant cancers.

Based on these data, we are evaluating an expansion cohort that includes two arms evaluating SY-5609 in combination with chemotherapy for the treatment of pancreatic cancer, one of which is evaluating SY-5609 in combination with gemcitabine in patients in first or second relapse who have progressed following treatment with the chemotherapy regimen known as FOLFIRINOX, and the other is exploring SY-5609 in combination with gemcitabine and nab-paclitaxel in patients following first relapse after FOLFIRINOX. SY-5609 is administered 7d on/7d off at a starting dose of 4 mg in both the gemcitabine combination and triplet combination arms, and the combination agents are administered at the approved doses. The study is designed to evaluate safety and tolerability, as well as efficacy measures such as progression free survival and disease control rate, or DCR, which is the combined rate of CR, partial response, or PR, and SD.

As of a October 12, 2022 safety data cut-off, a maximum tolerated dose, or MTD, of single agent SY-5609 administered in a 7 day on/7 day off dosing regimen has not been reached. The 10 mg dose level did not result in any dose limiting toxicities, or DLTs, further supporting the tolerability of the 7 day on/7 day off dosing regimen in which 30 patients have been dosed across five dose levels (4, 5, 6, 7, and 10 mg), with one DLT observed at the 4 mg single agent dose level. PK analyses demonstrated an expected increase in SY-5609 exposure levels, with the 10 mg single-agent dose also

supporting a preliminary exposure-response relationship. At the time of the October 20, 2022 clinical activity data-cut off, two of three study patients treated at the 10 mg single-agent dose level were response evaluable, with two of two response-evaluable patients achieving SD (one with pancreatic ductal adenocarcinoma, or PDAC, and one with colorectal cancer, or CRC), with the PDAC patient experiencing a 10% tumor reduction. As of the safety data cut-off, an MTD for either the doublet or the triplet has not been reached in the 7 day on/7 day off dosing regimen, with dosing of SY-5609 up to 5 mg in the doublet and up to 4 mg in the triplet regimen, respectively. SY-5609 has been combined with gemcitabine and with gemcitabine plus nab-paclitaxel, with no new safety signals identified and the majority of AEs being low grade and reversible. The most common related AEs in the cohort with SY-5609 and gemcitabine, where the highest SY-5609 doses were evaluated in combination with chemotherapy, included fatigue, nausea, decreased appetite and decreased platelet count (all low grade), with one patient experiencing a DLT of grade 3 diarrhea at the 5 mg SY-5609 dose level. No DLTs were reported in patients treated with SY-5609 in combination with gemcitabine/nab-paclitaxel. As of the clinical activity data cut-off, initial doublet activity of SY-5609 plus gemcitabine in PDAC included a confirmed PR by Response Evaluation Criteria in Solid Tumors, or RECIST, accompanied by a 98% reduction in the CA 19-9 tumor marker from a baseline of 60,357 U/mL to 968 U/mL, in one of four response evaluable patients treated at the 4 mg SY-5609 dose level, corresponding to a 25% DCR, and SD in three of four response evaluable patients treated at the 5 mg SY-5609 dose level, corresponding to a 75% DCR, for an overall DCR of 50% (four out of eight) in response evaluable patients. There is preliminary evidence for an exposure-response relationship, with the responding patient who achieved a confirmed PR demonstrating higher-than-average exposure relative to other patients at that dose. Two of three patients treated at the 4 mg dose level in the triplet regimen cohort were response evaluable, including one with SD. We have completed enrollment in the single agent cohort for select solid tumors and in the doublet combination cohort in PDAC patients, and we are currently seeking a partnership for the further development of SY-5609.

In August 2021, we announced entry into a clinical supply agreement with Roche, pursuant to which we agreed to supply SY-5609 for a combination dosing cohort with atezolizumab in Roche's ongoing Phase 1/1b INTRINSIC trial, which is evaluating multiple targeted therapies or immunotherapy, including atezolizumab, as single agents or in rational specified combinations in molecularly defined subsets of colorectal cancer patients. SY-5609 is being evaluated in combination with atezolizumab in patients with BRAF-mutant disease, and this arm of the trial is now actively enrolling. Under the terms of the agreement, Roche will sponsor and conduct the Phase 1/1b study to evaluate the safety, tolerability and preliminary efficacy of the combination of SY-5609 and atezolizumab and will assume all costs associated with the study. In exchange for providing SY-5609, we will receive access to the data on SY-5609 in combination with atezolizumab. We retain all rights to SY-5609.

Strategic Financing

On July 3, 2022, we entered into an Agreement and Plan of Merger, or the Merger Agreement, with Tack Acquisition Corp., a Delaware corporation and a wholly-owned subsidiary of us, or the Merger Sub, and Tyme Technologies, Inc., a Delaware corporation, or Tyme, providing for the merger of the Merger Sub with and into Tyme, with Tyme surviving the merger as our wholly-owned subsidiary, or the Merger. In connection with the closing of the Merger on September 16, 2022, we acquired net cash, cash equivalents and marketable securities of \$67.1 million, before deducting severance costs and other commitments entered into by Tyme management prior to the consummation of the Merger of approximately \$4.5 million.

Also on July 3, 2022, immediately prior to the execution and delivery of the Merger Agreement, we entered into a Securities Purchase Agreement with certain accredited investors, pursuant to which the investors agreed to purchase shares of our common stock and/or pre-funded warrants to purchase shares of our common stock, and accompanying warrants to purchase additional shares of our common stock (or pre-funded warrants in lieu thereof), or the PIPE Financing. On September 16, 2022, the PIPE Financing closed concurrently with the Merger. At the closing of the Merger, we issued an aggregate of 7,546,014 shares of our common stock to Tyme stockholders. In the PIPE Financing, we issued an aggregate of 6,387,173 shares of our common stock and, in lieu of shares to certain investors, pre-funded warrants to purchase an aggregate of 7,426,739 shares of common stock, and, in each case, accompanying warrants to purchase an aggregate of up to 13,813,912 additional shares of common stock (or pre-funded warrants to purchase common stock in lieu thereof). We received aggregate gross proceeds from the PIPE Financing of \$129.9 million, before deducting estimated offering expenses payable by us not inclusive of any exercise of the warrants.

Financial Operations Overview

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the foreseeable future. For the year ended December 31, 2022, we recognized \$14.9 million of revenue, \$13.6 million of which was related to our collaboration with GBT and \$1.3 million of which was related to our target discovery collaboration with Incyte. For the year ended December 31, 2021, we recognized \$23.5 million of revenue, \$19.4 million of which was related to our collaboration with GBT and \$4.1 million of which was related to our target discovery collaboration with Incyte. For the year ended December 31, 2020, we recognized \$15.1 million of revenue, \$11.7 million of which was attributable to our collaboration with GBT and \$3.4 million of which was attributable to our target discovery collaboration with Incyte.

Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including development of our gene control platform and the development of our product candidates, which include:

- employee-related expenses, including salaries and benefits;
- stock-based compensation expense;
- external costs of funding activities performed by third parties that conduct research and development on our behalf and of purchasing supplies used in designing, developing and manufacturing preclinical study and clinical trial materials;
- consulting, licensing and professional fees related to research and development activities; and
- facilities costs, depreciation and amortization and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other operating costs.

Research and development costs are expensed as incurred. Nonrefundable advance payments made to vendors for goods or services that will be received in the future for use in research and development activities are deferred and capitalized, even when there is no alternative future use for the research and development, until related goods or services are provided.

We typically use our employee, consultant and infrastructure resources across our research and development programs. We track outsourced development costs by product candidate or development program, but we do not allocate personnel costs, other internal costs or certain external consultant costs to specific product candidates or development programs. Based on our current operating plans, we expect that our future research and development expenses relating to our preclinical and drug discovery programs will be reimbursable by our collaboration partners.

The following table summarizes our external research and development expenses by program, as well as expenses not allocated to programs, for the years ended December 31, 2022, 2021 and 2020 (in thousands):

| | | Year Ended December 31, | | |
|---|-------------------|----------------------------|------------------|--|
| | 2022 | 2021 | 2020 | |
| Tamibarotene external costs | \$ 41,549 | \$ 30,670 | \$ 12,175 | |
| SY-5609 and other CDK7 program external costs ⁽¹⁾ | 6,754 | 11,452 | 11,229 | |
| SY-2101 program external costs ⁽²⁾ | 4,211 | 3,947 | 12,062 | |
| Other research and platform program external costs | 15,658 | 17,134 | 10,996 | |
| Employee-related expenses, including stock-based compensation | 36,267 | 29,857 | 23,295 | |
| Facilities and other expenses | 7,505 | 6,812 | 6,308 | |
| Total research and development expenses | <u>\$ 111,944</u> | <u>\$ 99,872</u> | <u>\$ 76,065</u> | |

(1)Our SY-1365 clinical trial costs are included within this caption as part of our CDK7 programs. In October 2019 we announced our decision to discontinue further development of SY-1365, which was completed during the year ended December 31, 2020.

(2) In December 2020, we acquired SY-2101, a product candidate in development for the treatment of APL, from Orsenix. In connection with this acquisition, we made an up-front payment of \$12.0 million to Orsenix, which we recorded as research and development expenses.

We expect our research and development expenses will increase for the foreseeable future as we seek to advance our programs. At this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the development of our product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from sales of our product candidates. This is due to the numerous risks and uncertainties associated with developing such product candidates, including the uncertainty of:

- successful completion of preclinical studies, including activities related to preparation of investigational new drug applications, or INDs, and minimally efficacious dose studies in animals, where applicable and required, under the requirements of the FDA, or another regulatory authority;
- approval of INDs for our product candidates to commence planned or future clinical trials;
- successful enrollment in, and completion of, clinical trials;
- successful data from our clinical programs that support an acceptable benefit-risk profile of our product candidates in the intended populations;
- successful development, and subsequent clearance or approval, of companion diagnostic tests for use in identifying potential patients;
- receipt of regulatory approvals from applicable regulatory authorities;
- establishment of arrangements with third-party manufacturers for clinical supply and commercial manufacturing and, where applicable, commercial manufacturing capabilities;
- establishment and maintenance of patent and trade secret protection or regulatory exclusivity for our product candidates;
- commercial launch of our product candidates, if and when approved, whether alone or in collaboration with others;
- enforcement and defense of intellectual property rights and claims;
- maintenance of a continued acceptable safety profile of the product candidates following approval;
- retention of key research and development personnel;
- the continuing impact of the COVID-19 pandemic; and
- general economic conditions, including inflation, recession risk and increasing interest rates.

Any changes in the outcome of any of these variables with respect to the development of our product candidates in preclinical and clinical development could mean a significant change in the costs and timing associated with the development of these product candidates. For example, if the FDA or another regulatory authority were to delay our planned start of clinical trials or require us to conduct clinical trials or other testing beyond those that we currently expect or if we experience significant delays in enrollment in any of our planned clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development of our product candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, information technology and administrative functions. Other significant

costs include corporate facility costs not otherwise included in research and development expenses, legal fees related to patent and corporate matters, and fees for accounting and consulting services.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates.

Transaction Related Expenses

Transaction related expenses primarily consist of incurred costs allocated to the warrants issued in connection with the PIPE Financing that were accounted for as liabilities, and severance paid to former Tyme employees.

Interest Income

Interest income consists of interest income on our cash, cash equivalents, and investments in marketable securities, including the related amortization of premium and discounts.

Interest Expense

Interest expense consists of interest, amortization of debt discount, and amortization of deferred financing costs associated with our loans payable, and interest on finance lease arrangements.

Change in Fair Value of Warrant Liabilities

Change in fair value of warrant liabilities is the result of the remeasurement of the fair value of our warrant liabilities at each reporting period end.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP. The preparation of these financial statements requires us to make judgments and estimates that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances. Actual results may differ from these estimates under different assumptions or conditions. On an ongoing basis, we evaluate our judgments and estimates in light of changes in circumstances, facts and experience. The effects of material revisions in estimates, if any, will be reflected in the financial statements prospectively from the date of the change in estimates.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this Annual Report, we believe the following accounting policies used in the preparation of our financial statements require the most significant judgments and estimates.

Revenue

To date our only revenue has consisted of collaboration and license revenue. We have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the foreseeable future. For the year ended December 31, 2022, we recognized \$14.9 million of revenue, \$13.6 million of which was related to our collaboration with GBT and \$1.3 million of which was related to our target discovery collaboration with Incyte. For the year ended December 31, 2021, we recognized \$23.5 million of revenue, \$19.4 million of which was related to our collaboration with GBT and \$4.1 million of which was related to our target discovery collaboration with Incyte. For the year ended December 31, 2020, we recognized \$15.1 million of revenue, \$11.7 million of which was related to our collaboration with GBT and \$3.4 million of which was related to our target discovery collaboration with Incyte.

We recognize revenue in conformity with Accounting Standards Codification, or ASC, *Revenue from Contracts with Customers*, or ASC 606. ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the

consideration the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps:

- (i) identify the contract(s) with a customer;
- (ii) identify the performance obligations in the contract;
- (iii) determine the transaction price;
- (iv) allocate the transaction price to the performance obligations in the contract; and
- (v) recognize revenue when (or as) the entity satisfies a performance obligation.

We only apply the five-step model to contracts when it is probable that we will collect the consideration to which we are entitled in exchange for the goods or services we transfer to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations, and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

From time to time, we may enter into agreements that are within the scope of ASC 606. The terms of these arrangements typically include payment to us of one or more of the following: non-refundable, up-front license fees, prepaid research and development services, development, regulatory and commercial milestone payments; and royalties on net sales of licensed products. Each of these payments would result in license and collaboration revenues, except for revenues from royalties on net sales of licensed products, which will be classified as royalty revenues.

We analyze our collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements*, or ASC 808, to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to ASC 606. For those elements of the arrangement that are accounted for pursuant to ASC 606, we apply the five-step model described above.

Research and Development Expenses

Expenditures relating to research and development are expensed in the period incurred. Research and development expenses consist of both internal and external costs associated with the development of our gene control platform and product candidates. Research and development costs include salaries and benefits, materials and supplies, external research, preclinical and clinical development expenses, stock-based compensation expense and facilities costs. Facilities costs primarily include the allocation of rent, utilities, depreciation and amortization.

In certain circumstances, we are required to make nonrefundable advance payments to vendors for goods or services that will be received in the future for use in research and development activities. In such circumstances, the nonrefundable advance payments are deferred and capitalized, even when there is no alternative future use for the research and development, until related goods or services are provided.

We record accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, we analyze progress of the work being performed, including the phase or completion of the event, invoices received and costs. Significant judgements and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from our estimates.

We may in-license the rights to develop and commercialize product candidates. For each in-license transaction, we evaluate whether we have acquired processes or activities along with inputs that would be sufficient to constitute a "business"

as defined under U.S. GAAP. A “business” as defined under U.S. GAAP consists of inputs and processes applied to those inputs that have the ability to create outputs. Although businesses usually have outputs, outputs are not required for an integrated set of activities to qualify as a business. When we determine that we have not acquired sufficient processes or activities to constitute a business, any up-front payments, as well as milestone payments, are immediately expensed as acquired research and development in the period in which they are incurred.

Warrants

We account for our issued warrants as either liability or equity in accordance with ASC 480-10, *Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity*, or ASC 480-10, or ASC 815-40, *Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock*, or ASC 815-40. Under ASC 480-10, warrants are considered liabilities if they are mandatorily redeemable and they require settlement in cash or other assets, or a variable number of shares. If warrants do not meet liability classification under ASC 480-10, we consider the requirements of ASC 815-40 to determine whether the warrants should be classified as liability or equity. Under ASC 815-40, contracts that may require settlement for cash are liabilities, regardless of the probability of the occurrence of the triggering event. Liability classified warrants are measured at fair value on the issuance date and at the end of each reporting period. Any change in the fair value of the warrants after the issuance date is recorded in the consolidated statements of operations as a gain or loss. If warrants do not require liability classification under ASC 815-40, in order to conclude warrants should be classified as equity, the Company assesses whether the warrants are indexed to its common stock and whether the warrants are classified as equity under ASC 815-40 or other applicable GAAP. Equity classified warrants are accounted for at fair value on the issuance date with no changes in fair value recognized after the issuance date.

On September 16, 2022, through the PIPE Financing, we issued 6,387,173 shares of common stock, and, in lieu of shares of common stock, pre-funded warrants to purchase an aggregate of 7,426,739 shares of common stock, or the 2022 Pre-Funded Warrants, and, in each case, accompanying warrants, or the 2022 Warrants, to purchase an aggregate of up to 13,813,912 additional shares of common stock (or 2022 Pre-Funded Warrants to purchase common stock in lieu thereof) at a price of \$10.34 per share and accompanying 2022 Warrant (or \$10.33 per 2022 Pre-Funded Warrant and accompanying 2022 Warrant). The PIPE Financing resulted in aggregate gross proceeds of \$129.9 million, before \$10.1 million of transaction costs.

On December 8, 2020, through a private placement, we issued 1,031,250 shares of our common stock and, in lieu of common stock, pre-funded warrants to purchase an aggregate of 100,000 shares of common stock, or the 2020 Pre-Funded Warrants, and, in each case, accompanying warrants, or the 2020 Warrants, to purchase an aggregate of up to 282,812 additional shares of common stock (or 2020 Pre-Funded Warrants to purchase common stock in lieu thereof) at a price of \$80.00 per share and accompanying warrant (or \$79.90 per pre-funded warrant and accompanying warrant). The private placement resulted in aggregate gross proceeds of \$90.5 million, before \$0.4 million of transaction costs.

In the event of certain fundamental transactions involving the Company, the holders of 2022 Warrants and 2020 Warrants may require us to make a payment based on a Black-Scholes valuation, using specified inputs. The holders of 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants do not have similar rights. Therefore, we accounted for the 2022 Warrants and 2020 Warrants as liabilities, while the 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants met the permanent equity criteria classification. The 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants are classified as a component of permanent equity because they are freestanding financial instruments that are legally detachable and separately exercisable from the shares of common stock with which they were issued, are immediately exercisable, do not embody an obligation for us to repurchase our shares, and permit the holders to receive a fixed number of shares of common stock upon exercise. In addition, the 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants do not provide any guarantee of value or return. The initial fair value of the 2022 Warrants and 2020 Warrants was \$64.7 million and \$19.3 million, respectively, determined using the Black-Scholes valuation model. We remeasured the aggregate fair value of the 2022 Warrants and 2020 Warrants at December 31, 2022 and 2021 as \$24.5 million and \$3.0 million, respectively. The change in fair value of \$43.2 million (gain), \$16.7 million (gain), and \$0.4 million (loss) was recorded in our statement of operations for the years ended December 31, 2022, 2021, and 2020 respectively.

Stock-Based Compensation

We account for our stock-based compensation awards in accordance with ASC 718, *Compensation—Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees and directors, including grants of restricted stock units and stock option awards, to be recognized as expense in the consolidated statements of operations based on their grant date fair values.

We estimate the fair value of stock options granted using the Black-Scholes option-pricing model. Prior to June 30, 2016, we were a private company and, therefore, lack company-specific historical and implied volatility information. As a result, we estimate our expected stock volatility based on a combination of our historical volatility and that of a publicly traded set of peer companies. The expected term of our stock options has been determined utilizing the “simplified” method for awards that qualify as “plain-vanilla” options. The expected term of stock options to non-employees can be determined using either the contractual term of the option award or the “simplified” method. We elected to continue to use the contractual term in determining the expected term of stock option to non-employees. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that we have never paid cash dividends and do not expect to pay any cash dividends in the foreseeable future. We use the value of our common stock to determine the fair value of restricted stock awards.

We expense the fair value of our stock-based awards to employees and non-employees on a straight-line basis over the associated service period, which is generally the vesting period. We account for forfeitures as they occur instead of estimating forfeitures at the time of grant. Ultimately, the actual expense recognized over the vesting period will be for only those options that vest.

Compensation expense for discounted purchases under the employee stock purchase plan is measured using the Black-Scholes model to compute the fair value of the lookback provision plus the purchase discount and is recognized as compensation expense over the offering period.

For stock-based awards that contain performance-based milestones, we record stock-based compensation expense in accordance with the accelerated attribution model. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. For certain of our performance-based awards, notwithstanding any vesting in accordance with the achievement of performance-based milestones, such awards vest in full on the sixth anniversary of the vesting commencement date. Compensation expense for such awards is recognized over the six-year vesting period unless management determines that the achievement of any performance-based milestones is probable, in which case expense is accelerated. Compensation expense related to these awards were all recognized as of December 31, 2020 as the performance-based milestones were achieved.

We have computed the fair value of stock options at the date of grant using the following weighted-average assumptions:

| | Year Ended December 31, | | | | | |
|--|-------------------------|---|-------|---|-------|---|
| | 2022 | | 2021 | | 2020 | |
| Weighted-average risk-free interest rate | 3.56 | % | 0.99 | % | 1.28 | % |
| Expected dividend yield | — | % | — | % | — | % |
| Expected option term (in years) | 5.80 | | 6.03 | | 5.99 | |
| Volatility | 83.32 | % | 81.56 | % | 78.27 | % |

Results of Operations

Comparison of Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021, together with the changes in those items in dollars (in thousands):

| | Year Ended December 31, | | | |
|---|-------------------------|---------------------|--------------------|------------|
| | 2022 | 2021 | Dollar Change | % Change |
| Statements of Operations Data: | | | | |
| Revenue | \$ 14,880 | \$ 23,488 | \$ (8,608) | (37) % |
| Operating expenses: | | | | |
| Research and development | 111,944 | 99,872 | 12,072 | 12 % |
| General and administrative | 29,299 | 23,036 | 6,263 | 27 % |
| Transaction related expenses | 9,510 | - | 9,510 | 100 % |
| Total operating expenses | 150,753 | 122,908 | 27,845 | 23 % |
| Loss from operations | (135,873) | (99,420) | (36,453) | 37 % |
| Interest income | 2,132 | 87 | 2,045 | 2,351 % |
| Interest expense | (4,134) | (3,907) | (227) | 6 % |
| Change in fair value of warrant liabilities | 43,221 | 16,682 | 26,539 | 159 % |
| Net loss | <u>\$ (94,654)</u> | <u>\$ (86,558)</u> | <u>\$ (8,096)</u> | <u>9 %</u> |

Revenue

For the year ended December 31, 2022, we recognized approximately \$14.9 million of revenue, \$13.6 million of which was attributable to our collaboration with GBT and \$1.3 million of which was attributable to our target discovery collaboration with Incyte. For the year ended December 31, 2021, we recognized approximately \$23.5 million of revenue, \$19.4 million of which was attributable to our collaboration with GBT and \$4.1 million of which was attributable to our target discovery collaboration with Incyte.

Research and Development Expense

Research and development expense increased by approximately \$12.1 million, or 12%, from \$99.9 million for the year ended December 31, 2021 to \$111.9 million for the year ended December 31, 2022. The following table summarizes our research and development expenses for the years ended December 31, 2022 and 2021, together with the changes to those items in dollars (in thousands):

| | Year Ended December 31, | | | |
|---|-------------------------|------------------|------------------|-------------|
| | 2022 | 2021 | Dollar Change | % Change |
| External research and development | \$ 61,370 | \$ 56,809 | \$ 4,561 | 8 % |
| Employee-related expenses, excluding stock-based compensation | 30,321 | 24,151 | 6,170 | 26 % |
| Stock-based compensation | 5,946 | 5,706 | 240 | 4 % |
| Consulting, licensing and professional fees | 6,802 | 6,394 | 408 | 6 % |
| Facilities and other expenses | 7,505 | 6,812 | 693 | 10 % |
| Total research and development expenses | <u>\$ 111,944</u> | <u>\$ 99,872</u> | <u>\$ 12,072</u> | <u>12 %</u> |

The change in research and development expense was primarily attributable to research and development activities associated with advancing our lead clinical and preclinical programs and enhancing our internal capabilities, and included the following:

- an increase of approximately \$4.6 million, or 8%, in external research and development, primarily attributable to the increases in costs associated with the continued advancement of our existing clinical trials of tamibarotene;

- an increase of approximately \$6.2 million, or 26%, for employee-related expenses, including increased salary and benefits primarily due to our annual merit increase and hiring of more senior roles;
- an increase of approximately \$0.4 million, or 6%, for consulting, licensing and professional fees, primarily related to the advancement of our clinical trials of tamibarotene;
- an increase of approximately \$0.2 million, or 4%, for stock-based compensation, primarily due to special grants awarded to our employees; and
- an increase of approximately \$0.7 million, or 10%, in facilities and other expenses primarily due to the rent expense related to the lease for our headquarters and software subscriptions used for our research and development activities.

General and Administrative Expense

General and administrative expense increased by approximately \$6.3 million, or 27%, from \$23.0 million for the year ended December 31, 2021 to \$29.3 million for the year ended December 31, 2022. The change in general and administrative expense was primarily attributable to an increase in employee-related expenses and an increase in recruiting fees.

Transaction Related Expenses

Transaction related expenses primarily consist of incurred costs allocated to the warrants issued in connection with the PIPE Financing that were accounted for as liabilities, and severance paid to former Tyme employees.

Interest Income

Interest income was derived generally from our investments in cash, cash equivalents and marketable securities. The increase in interest income during the year ended December 31, 2022 as compared to the year ended December 31, 2021 was due to additional cash and marketable securities from the PIPE Financing and the Merger and higher interest rates in 2022 compared to 2021.

Interest Expense

Interest expense was related to our credit facility with Oxford Finance LLC, or Oxford, and equipment financing arrangements. Interest expense increased during the year ended December 31, 2022 as compared to the year ended December 31, 2021 due to a higher average carrying value of the credit facility and the increasing interest rates during the year ended December 31, 2022 compared to the year ended December 31, 2021.

Change in Fair Value of Warrant Liabilities

The change in fair value of warrant liabilities during the year ended December 31, 2022 as compared to the year ended December 31, 2021 was a result of the remeasurement of the fair value of warrants issued in connection with the September 2022 and December 2020 private placements.

Comparison of Years Ended December 31, 2021 and 2020

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020, together with the changes in those items in dollars (in thousands):

| | Year Ended December 31, | | | |
|---|-------------------------|--------------|---------------|----------|
| | 2021 | 2020 | Dollar Change | % Change |
| Statements of Operations Data: | | | | |
| Revenue | \$ 23,488 | \$ 15,093 | \$ 8,395 | 56 % |
| Operating expenses: | | | | |
| Research and development | 99,872 | 76,065 | 23,807 | 31 % |
| General and administrative | 23,036 | 21,325 | 1,711 | 8 % |
| Total operating expenses | 122,908 | 97,390 | 25,518 | 26 % |
| Loss from operations | (99,420) | (82,297) | (17,123) | 21 % |
| Interest income | 87 | 426 | (339) | (80) % |
| Interest expense | (3,907) | (1,792) | (2,115) | 118 % |
| Change in fair value of warrant liabilities | 16,682 | (375) | 17,057 | 4,549 % |
| Net loss | \$ (86,558) | \$ (84,038) | \$ (2,520) | 3 % |

Revenue

For the year ended December 31, 2021, we recognized approximately \$23.5 million of revenue, \$19.4 million of which was attributable to our collaboration with GBT and \$4.1 million of which was attributable to our target discovery collaboration with Incyte. For the year ended December 31, 2020, we recognized \$15.1 million of revenue, \$11.7 million of which was attributable to our collaboration with GBT and \$3.4 million of which was attributable to our target discovery collaboration with Incyte.

Research and Development Expense

Research and development expense increased by approximately \$23.8 million, or 31%, from \$76.1 million for the year ended December 31, 2020 to \$99.9 million for the year ended December 31, 2021. The following table summarizes our research and development expenses for the years ended December 31, 2021 and 2020, together with the changes to those items in dollars (in thousands):

| | Year Ended December 31, | | | |
|---|-------------------------|-----------|---------------|----------|
| | 2021 | 2020 | Dollar Change | % Change |
| External research and development | \$ 56,809 | \$ 42,981 | \$ 13,828 | 32 % |
| Employee-related expenses, excluding stock-based compensation | 24,151 | 18,563 | 5,588 | 30 % |
| Stock-based compensation | 5,706 | 4,732 | 974 | 21 % |
| Consulting, licensing and professional fees | 6,394 | 3,481 | 2,913 | 84 % |
| Facilities and other expenses | 6,812 | 6,308 | 504 | 8 % |
| Total research and development expenses | \$ 99,872 | \$ 76,065 | \$ 23,807 | 31 % |

The change in research and development expense was primarily attributable to research and development activities associated with advancing our lead clinical and preclinical programs and enhancing our internal capabilities, and included the following:

- an increase of approximately \$13.8 million, or 32%, in external research and development, primarily attributable to the increases in costs associated with the continued advancement of our existing clinical trials of tamibarotene, SY-2101 and SY-5609 and advancement of our preclinical programs, including our sickle cell disease development activities in collaboration with GBT;
- an increase of approximately \$5.6 million, or 30%, for employee-related expenses, including increased salary and benefits primarily due to our increased headcount;
- an increase of approximately \$2.9 million, or 84%, for consulting, licensing and professional fees, primarily related to the advancement of our clinical and pre-clinical programs;
- an increase of approximately \$1.0 million, or 21%, for stock-based compensation, also primarily due to our increased headcount; and

- an increase of approximately \$0.5 million, or 8%, in facilities and other expenses primarily due to the rent expense related to the lease for our headquarters.

General and Administrative Expense

General and administrative expense increased by approximately \$1.7 million, or 8%, from \$21.3 million for the year ended December 31, 2020 to \$23.0 million for the year ended December 31, 2021. The change in general and administrative expense was primarily attributable to an increase in employee-related expenses driven by increased headcount, COVID-19 testing expenses incurred by us to support the health and safety of our employees, an increase in legal costs including patent prosecution expenses, and an increase in consulting fees.

Interest Income

Interest income was derived from our investments in cash, cash equivalents and marketable securities. The decrease in interest income during the year ended December 31, 2021 as compared to the year ended December 31, 2020 was due to lower yield on our investments in cash, cash equivalents and marketable securities due to capital market conditions during the year ended December 31, 2021.

Interest Expense

Interest expense was related to our credit facility with Oxford and equipment financing arrangements. The increase in interest expense during the year ended December 31, 2021 as compared to the year ended December 31, 2020 was driven by a higher average outstanding balance of our credit facility with Oxford during the year ended December 31, 2021 compared to the year ended December 31, 2020.

Change in Fair Value of Warrant Liabilities

The increase in the change in fair value of warrant liabilities during the year ended December 31, 2021 as compared to the year ended December 31, 2020 was a result of the remeasurement of the fair values of warrants issued in connection with the private placement financing in December 2020.

Liquidity and Capital Resources

Sources of Liquidity

We funded our operations from inception through December 31, 2022 primarily through the sale of equity securities, through license and collaboration agreements, including those with Incyte and GBT, and through the credit facility with Oxford.

On July 3, 2022, we entered into the Merger Agreement with Tyme. Also on July 3, 2022, immediately prior to the execution and delivery of the Merger Agreement, we entered into the Securities Purchase Agreement with certain accredited investors.

In connection with the closing of the Merger on September 16, 2022, we acquired net cash, cash equivalents and marketable securities of \$67.1 million, before deducting severance costs and other commitments entered into by Tyme management prior to the consummation of the Merger of approximately \$4.5 million. The PIPE Financing closed concurrently with the Merger on September 16, 2022, pursuant to which we received aggregate gross proceeds of \$129.9 million, before deducting offering expenses payable by us, and not inclusive of any exercise of the warrants issued in the PIPE Financing.

On February 12, 2020, we entered into the Loan Agreement with Oxford. Pursuant to the Loan Agreement, a term loan of up to an aggregate principal amount of \$60.0 million is available to us. A \$20.0 million term loan was funded on February 12, 2020, and another \$20.0 million term loan was funded on December 23, 2020. On July 3, 2022, we entered into an amendment to the Loan Agreement with Oxford, or the Loan Amendment. Pursuant to the Loan Amendment, Oxford has agreed to modify the Loan Agreement in order to, among other things, extend the interest only period from March 1, 2023 to March 1, 2024 and extend the maturity date from February 1, 2025 to February 1, 2026, and upon the achievement of certain milestones and subject to the payment of certain fees, further extend the interest only period to September 1, 2024 and

maturity date to August 1, 2026. As of December 31, 2022, \$20.0 million remains available under the Loan Agreement, at the sole discretion of Oxford.

On June 12, 2020, we filed a universal shelf registration statement on Form S-3 with the SEC to register for sale from time to time up to \$300.0 million of common stock, preferred stock, debt securities, warrants and/or units in one or more registered offerings. The registration statement was declared effective on June 22, 2020. Further, in June 2020, we entered into an at-the-market sales agreement, or the 2020 sales agreement, with Cowen and Company, LLC, or Cowen, pursuant to which we may offer and sell shares of our common stock having an aggregate offering price of up to \$75.0 million through Cowen pursuant to the registration statement. We did not issue any shares of common stock pursuant to the 2020 sales agreement during the years ended December 31, 2022 or December 31, 2021. In January 2021, we issued shares of our common stock in an underwritten public offering resulting in gross proceeds of \$75.6 million, before deducting underwriting discounts and commissions and other transaction expenses of approximately \$5.1 million, pursuant to the Form S-3 that was filed with the SEC on June 12, 2020.

As of December 31, 2022, \$75.0 million of our common stock remained available for future issuance under the 2020 sales agreement.

As of December 31, 2022, \$224.4 million of securities remained available for issuance under the shelf registration statement.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of approximately \$202.3 million.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2022, 2021 and 2020 (in thousands):

| | Year Ended December 31, | | |
|---|-------------------------|---------------------|-------------------|
| | 2022 | 2021 | 2020 |
| Net cash (used in) provided by: | | | |
| Operating activities | \$ (123,065) | \$ (99,540) | \$ (57,364) |
| Investing activities | 67,185 | (52,653) | 46,664 |
| Financing activities | 131,045 | 70,511 | 142,953 |
| Net (decrease) increase in cash, cash equivalents and restricted cash | <u>\$ 75,165</u> | <u>\$ (81,682)</u> | <u>\$ 132,253</u> |

Net Cash Used in Operating Activities

The use of cash in operating activities in all periods presented resulted primarily from our net losses adjusted for non-cash charges and changes in components of working capital.

Net cash used in operating activities was \$123.1 million during the year ended December 31, 2022, compared to \$99.5 million during the year ended December 31, 2021. The increase in cash used in operating activities was primarily due to a \$36.5 million increase in the loss from operations during the year ended December 31, 2022, partially offset by an increase in interest income of \$2.0 million, an increase in stock-based compensation of \$1.0 million, transactions cost allocated to warrants issued in connection with the PIPE Financing of \$5.0 million, and a decrease in net operating assets and liabilities of \$5.1 million.

Net cash used in operating activities was \$99.5 million during the year ended December 31, 2021, compared to \$57.4 million during the year ended December 31, 2020. The increase in cash used in operating activities was primarily due to a \$17.1 million increase in loss from operations during the year ended December 31, 2021 and a \$20.0 million collection of the advanced payment pursuant to our collaboration agreement with GBT during the year ended December 31, 2020, which did not recur during the year ended December 31, 2021.

Net Cash Provided by (Used in) Investing Activities

Net cash provided by investing activities was \$67.2 million during the year ended December 31, 2022, compared to net cash used in investing activities of \$52.7 million during the year ended December 31, 2021. The net cash provided by

investing activities during the year ended December 31, 2022 was primarily due to maturities of our investment in marketable securities of \$68.4 million, partially offset by the purchase of \$1.2 million of property and equipment. Net cash used in investing activities during the year ended December 31, 2021 was primarily due to our reinvestment of \$51.4 million of our funds from cash equivalents into marketable securities and the purchase of \$1.2 million of property and equipment. Net cash provided by investing activities during the year ended December 31, 2020 was primarily due to maturities of our investment in marketable securities of \$50.0 million, partially offset by our \$3.3 million purchase of property and equipment.

Net Cash Provided by Financing Activities and Merger

Net cash provided by financing activities was \$131.0 million during the year ended December 31, 2022, compared to net cash provided by financing activities of \$70.5 million during the year ended December 31, 2021 and net cash provided by financing activities of \$143.0 million during the year ended December 31, 2020. Cash provided by financing activities for the year ended December 31, 2022 was primarily due to \$119.8 million of proceeds from the issuance of common stock and accompanying 2022 Warrants and 2022 Pre-Funded Warrants in the PIPE Financing, net of issuance costs and \$11.7 million of proceeds from the Merger (recapitalization), net of issuance costs, and \$0.2 million from the issuance of common stock through our employee stock purchase plan, partially offset by the payment of \$0.3 million to Oxford related to the Loan Amendment, \$0.3 million of payments made under our financing lease, and payment of \$0.1 million in lieu of fractional shares due to the reverse stock split of our common stock. Cash provided by financing activities for the year ended December 31, 2021 of \$70.5 million was the result of net proceeds of \$70.3 million from an underwritten public offering of shares of our common stock, \$0.2 million from the issuance of shares of our common stock through our 2016 Stock Incentive Plan and \$0.3 million from the issuance of common stock through our employee stock purchase plan, offset by payments of \$0.3 million under our capital lease obligations.

Cash provided by financing activities for year ended December 31, 2020 of \$143.0 million was the result of net proceeds of \$39.6 million drawn from our credit facility with Oxford, \$90.4 million from the issuance of securities in the December 2020 private placement, \$11.9 million from the issuance of shares of our common stock pursuant to the 2017 sales agreement, \$1.1 million from the issuance of shares of our common stock through our 2015 Stock Incentive Plan and \$0.4 million from issuance of common stock through our employee stock purchase plan, offset by payments of \$0.2 million under our capital lease obligations and payments of \$0.2 million of offering costs.

Material Cash Requirements from Known Contractual Obligations

Our material cash requirements from known contractual obligations as of December 31, 2022 consisted of:

- Principal and interest payments under our loan and security agreement with Oxford. For additional information regarding the terms of the debt and interest payable, see Note 7 to the consolidated financial statements in Item 8 of this Annual Report.
- Operating lease liabilities with respect to our lease of approximately 52,859 square feet of space in Cambridge, Massachusetts for a lease term ending in February 2030. For additional information regarding the terms of this operating lease, see Note 11 to the consolidated financial statements in Item 8 of this Annual Report.
- Contingent milestone obligations that may become payable pursuant to the asset purchase agreement with Orsenix. For additional information regarding these contingent milestone obligations, see Note 10 to the consolidated financial statements in Item 8 of this Annual Report.
- Obligations pursuant to our license agreement and supply management agreement with TMRC Co. Ltd, or TMRC. For additional information regarding these obligations, see Note 11 to the consolidated financial statements in Item 8 of this Annual Report.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue to advance our clinical trials of tamibarotene, SY-2101 and SY-5609, seek to develop companion diagnostic tests for use with our product candidates, initiate new research and preclinical development projects and seek marketing approval for any product candidates that we successfully develop. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to establishing sales, marketing, distribution and other

commercial infrastructure to commercialize such products. We will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on favorable terms, we would be forced to delay, reduce, eliminate, or out-license our research and development programs or future commercialization rights to our product candidates.

We believe that our cash, cash equivalents and marketable securities as of December 31, 2022, will enable us to fund our planned operating expense and capital expenditure requirements into the second quarter of 2025. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of tamibarotene, SY-2101 and SY-5609 and any associated companion diagnostic tests;
- research and preclinical development efforts for any future product candidates that we may develop;
- the number of future product candidates that we pursue and their development requirements;
- our ability to enter into, and the terms and timing of, any collaborations, licensing agreements or other arrangements;
- whether a drug candidate will be nominated to enter into investigational new drug application-enabling studies under our sickle cell disease collaboration with GBT, whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U.S. co-promotion option under the GBT agreement;
- whether our target discovery collaboration with Incyte will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the collaboration agreement with Incyte will ever be paid;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs of commercialization activities for any of our product candidates that receive marketing approval to the extent such costs are not the responsibility of any collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- the costs of acquiring potential new product candidates or technology;
- the costs of any physician education programs relating to selecting and treating genomically defined patient populations;
- the timing and amount of milestone and other payments due to licensors for patent and technology rights used in our gene control platform or to TMRC associated with the development, manufacture and commercialization of tamibarotene;
- the timing and amount of milestone payments due to Orsenix associated with the development and commercialization of SY-2101;
- revenue received from commercial sales, if any, of our current and future product candidates;
- our headcount growth and associated costs as we advance our clinical pipeline and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims; and
- the continuing impact of the COVID-19 pandemic.

Identifying potential product candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes many years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our common stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise funds through additional collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risk related to changes in interest rates. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments, including cash equivalents, are in the form of money market funds and marketable securities and are invested in U.S. treasury or government obligations. However, because of the short-term nature of the duration of our portfolio and the low-risk profile of our investments, we believe an immediate 10% change in market interest rates would not be expected to have a material impact on the fair market value of our investments portfolio or on our financial condition or results of operations.

We are also exposed to market risk related to changes in foreign currency exchange rates. We contract with vendors that are located in Asia and Europe and certain invoices are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these arrangements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2022, we had no significant liabilities denominated in foreign currencies.

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the year ended December 31, 2022.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

SYROS PHARMACEUTICALS, INC.
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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Syros Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Syros Pharmaceuticals, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity and cash flows for each of the three years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, in conformity with US generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Collaboration revenue recognition

Description of the Matter

As of December 31, 2022, the Company's revenue recorded under the collaboration agreement with Global Blood Therapeutics, Inc. totaled \$13.6 million. Additionally, the Company's related deferred revenue totaled \$4.3 million, all of which was current. As discussed in Note 4 to the consolidated financial statements, the Company recognizes revenue associated with each performance obligation as the research and development services are provided measured based on the ratio of costs incurred to date to the total estimated costs at completion.

Determining the estimated costs at completion is especially challenging because it requires the Company to forecast costs associated with internal employee efforts, materials costs, and third-party contract costs, as well as the assumed timing and duration of these activities. Due to uncertainties attributed to such factors, auditing the amount of revenue recognized from collaboration agreements involved especially challenging, subjective and complex judgments.

How We Addressed the Matter in Our Audit

To test the amount of revenue recognized in the current period from collaboration agreements and the balance of deferred revenue, we performed audit procedures that included, among others, reviewing minutes of meetings held with collaboration partners for any changes to key assumptions used. We obtained and inspected the agreements and amendments to test the existence of customer arrangements and understand the scope and pricing of the related projects. We also evaluated management's estimates of total costs expected to be incurred and the estimated timeframe over which costs are to be incurred by making direct inquiries of the Company's research and development personnel overseeing the projects, comparing cost estimates to costs previously incurred for similar activities, inspecting evidence of actual costs incurred and by performing analytical procedures. We recalculated the revenue recognized for the period based on the ratio of costs incurred to estimated total costs at completion of the research and development services and the transaction price.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.

Boston, Massachusetts
March 2, 2023

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share data)

| | December 31, 2022 | December 31, 2021 |
|--|----------------------|----------------------|
| Assets | | |
| Current assets: | | |
| Cash and cash equivalents | \$ 167,467 | \$ 92,302 |
| Marketable securities | 34,837 | 38,067 |
| Contract assets | 1,694 | 2,979 |
| Prepaid expenses and other current assets | 7,394 | 3,237 |
| Total current assets | 211,392 | 136,585 |
| Property and equipment, net | 11,353 | 12,844 |
| Marketable securities - noncurrent | — | 13,038 |
| Other long-term assets | 5,348 | 2,941 |
| Restricted cash | 3,086 | 3,086 |
| Right-of-use asset – operating lease | 13,231 | 14,104 |
| Right-of-use assets – financing leases | 76 | 337 |
| Total assets | <u>\$ 244,486</u> | <u>\$ 182,935</u> |
| Liabilities and stockholders' equity | | |
| Current liabilities: | | |
| Accounts payable | \$ 6,411 | \$ 3,692 |
| Accrued expenses | 17,966 | 15,624 |
| Deferred revenue, current portion | 4,330 | 10,181 |
| Financing lease obligations, current portion | 65 | 291 |
| Operating lease obligation, current portion | 2,006 | 1,720 |
| Total current liabilities | 30,778 | 31,508 |
| Financing lease obligations, net of current portion | — | 65 |
| Operating lease obligation, net of current portion | 20,851 | 22,858 |
| Warrant liabilities | 24,472 | 3,029 |
| Debt, net of debt discount, long term | 40,649 | 40,257 |
| Commitments and contingencies (See Note 10) | | |
| Stockholders' equity: | | |
| Preferred stock, \$0.001 par value; 10,000,000 shares authorized at December 31, 2022 and December 31, 2021; 0 shares issued and outstanding at December 31, 2022 and December 31, 2021 | — | — |
| Common stock, \$0.001 par value; 70,000,000 and 20,000,000 shares authorized at December 31, 2022 and December 31, 2021, respectively; 20,263,116 and 6,202,403 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively | 20 | 6 |
| Additional paid-in capital | 685,847 | 548,870 |
| Accumulated other comprehensive loss | 102 | (79) |
| Accumulated deficit | (558,233) | (463,579) |
| Total stockholders' equity | 127,736 | 85,218 |
| Total liabilities and stockholders' equity | <u>\$ 244,486</u> | <u>\$ 182,935</u> |

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except share and per share data)

| | | Year Ended December 31, | |
|---|---------------------|----------------------------|---------------------|
| | 2022 | 2021 | 2020 |
| Revenue | \$ 14,880 | \$ 23,488 | \$ 15,093 |
| Operating expenses: | | | |
| Research and development | 111,944 | 99,872 | 76,065 |
| General and administrative | 29,299 | 23,036 | 21,325 |
| Transaction related expenses | 9,510 | — | — |
| Total operating expenses | 150,753 | 122,908 | 97,390 |
| Loss from operations | (135,873) | (99,420) | (82,297) |
| Interest income | 2,132 | 87 | 426 |
| Interest expense | (4,134) | (3,907) | (1,792) |
| Change in fair value of warrant liabilities | 43,221 | 16,682 | (375) |
| Net loss applicable to common stockholders | <u>\$ (94,654)</u> | <u>\$ (86,558)</u> | <u>\$ (84,038)</u> |
| Net loss per share applicable to common stockholders - basic and diluted | <u>\$ (7.49)</u> | <u>\$ (13.84)</u> | <u>\$ (18.20)</u> |
| Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted | <u>12,631,968</u> | <u>6,253,498</u> | <u>4,605,162</u> |

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)

| | 2022 | Year Ended December 31, 2021 | 2020 |
|---|---------------------|------------------------------------|---------------------|
| Net loss | \$ (94,654) | \$ (86,558) | \$ (84,038) |
| Other comprehensive gain (loss): | | | |
| Unrealized holding gain (loss) on marketable securities | 181 | (79) | (24) |
| Comprehensive loss | <u>\$ (94,473)</u> | <u>\$ (86,637)</u> | <u>\$ (84,062)</u> |

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY
(in thousands except share data)

| | Common Stock | | | | Additional | | Accumulated | | Accumulated | Stockholders' |
|--|-------------------|--------------|-----------|----------------|------------|--------------|---------------|-------------------|-------------|----------------|
| | Number of | Par | | | Paid-In | | Other | | Deficit | Equity |
| | Shares | Value | | | Capital | | Comprehensive | | | |
| | | | | | | | (Loss) Gain | | | |
| Balance at December 31, 2019 | 4,336,780 | \$ 4 | \$ | 372,139 | \$ | 24 | \$ | (292,983) | \$ | 79,184 |
| Exercise of stock options | 17,072 | — | | 1,076 | | — | | — | | 1,076 |
| Vesting of restricted stock units | 10,936 | — | | — | | — | | — | | — |
| Issuance of shares under Employee Stock Purchase Plan | 5,955 | — | | 433 | | — | | — | | 433 |
| Issuance of common stock at-the-market, net of issuance costs of \$411 | 220,181 | — | | 11,919 | | — | | — | | 11,919 |
| Issuance of common stock and accompanying Pre-funded warrants at private placement, net of issuance costs of \$401 | 1,031,250 | 1 | | 70,752 | | — | | — | | 70,753 |
| Issuance of warrants related to entering into debt arrangement | — | — | | 302 | | — | | — | | 302 |
| Exercise of warrants | 100 | — | | 9 | | — | | — | | 9 |
| Stock-based compensation expense | — | — | | 10,939 | | — | | — | | 10,939 |
| Other comprehensive loss | — | — | | — | | (24) | | — | | (24) |
| Net loss | — | — | | — | | — | | (84,038) | | (84,038) |
| Balance at December 31, 2020 | <u>5,622,274</u> | <u>\$ 5</u> | <u>\$</u> | <u>467,569</u> | <u>\$</u> | <u>—</u> | <u>\$</u> | <u>(377,021)</u> | <u>\$</u> | <u>90,553</u> |
| Exercise of stock options | 2,013 | — | | 157 | | — | | — | | 157 |
| Vesting of restricted stock units | 28,685 | — | | — | | — | | — | | — |
| Issuance of shares under Employee Stock Purchase Plan | 9,431 | — | | 323 | | — | | — | | 323 |
| Issuance of common stock in underwritten public offering, net of issuance costs of \$5,132 | 540,000 | 1 | | 70,467 | | — | | — | | 70,468 |
| Stock-based compensation expense | — | — | | 10,354 | | — | | — | | 10,354 |
| Other comprehensive loss | — | — | | — | | (79) | | — | | (79) |
| Net loss | — | — | | — | | — | | (86,558) | | (86,558) |
| Balance at December 31, 2021 | <u>6,202,403</u> | <u>\$ 6</u> | <u>\$</u> | <u>548,870</u> | <u>\$</u> | <u>(79)</u> | <u>\$</u> | <u>(463,579)</u> | <u>\$</u> | <u>85,218</u> |
| Exercise of stock options | 3,770 | — | | — | | — | | — | | — |
| Vesting of restricted stock units | 86,066 | 1 | | — | | — | | — | | 1 |
| Issuance of shares under Employee Stock Purchase Plan | 48,560 | — | | 217 | | — | | — | | 217 |
| Issuance of shares in private placement, net of issuance cost of \$5,068 | 6,387,173 | 6 | | 60,106 | | — | | — | | 60,112 |
| Issuance of shares in merger, net of issuance cost of \$3,136 | 7,546,014 | 7 | | 65,325 | | — | | — | | 65,332 |
| Cancellation of fractional shares due to reverse stock split | (10,870) | — | | (81) | | — | | — | | (81) |
| Stock-based compensation expense | — | — | | 11,410 | | — | | — | | 11,410 |
| Other comprehensive gain | — | — | | — | | 181 | | — | | 181 |
| Net loss | — | — | | — | | — | | (94,654) | | (94,654) |
| Balance at December 31, 2022 | <u>20,263,116</u> | <u>\$ 20</u> | <u>\$</u> | <u>685,847</u> | <u>\$</u> | <u>102</u> | <u>\$</u> | <u>(558,233)</u> | <u>\$</u> | <u>127,736</u> |

See accompanying notes to consolidated financial statements

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

| | 2022 | Year Ended December 31, 2021 | 2020 |
|--|--------------|------------------------------------|--------------|
| Operating activities | | | |
| Net loss | \$ (94,654) | \$ (86,558) | \$ (84,038) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | | |
| Depreciation and amortization | 2,706 | 2,758 | 2,774 |
| Amortization of right-of-use asset | 261 | 260 | 261 |
| Transaction costs allocated to warrants issued in connection with private placement | 5,015 | — | — |
| Stock-based compensation expense | 11,410 | 10,354 | 10,939 |
| Change in fair value of warrant liabilities | (43,221) | (16,682) | 375 |
| Net amortization of premiums and discounts on marketable securities | 243 | 224 | (49) |
| Amortization of debt-discount and accretion of deferred debt costs | 692 | 706 | 287 |
| Changes in operating assets and liabilities: | | | |
| Prepaid expenses and other current assets | (2,807) | (995) | 309 |
| Accounts receivable | — | 7 | 19,993 |
| Contract assets | 1,285 | (655) | (2,166) |
| Other long-term assets | (2,407) | (1,196) | (1,269) |
| Accounts payable | 2,766 | 48 | (1,057) |
| Accrued expenses | 2,345 | 4,830 | 593 |
| Deferred revenue | (5,851) | (11,905) | (6,292) |
| Proceeds for tenant improvement incentive from landlord | — | — | 2,035 |
| Operating lease asset and liabilities | (848) | (736) | (59) |
| Net cash used in operating activities | (123,065) | (99,540) | (57,364) |
| Investing activities | | | |
| Purchases of property and equipment | (1,241) | (1,245) | (3,336) |
| Purchases of marketable securities | — | (51,408) | — |
| Maturities of marketable securities | 68,426 | — | 50,000 |
| Net cash (used in) provided by investing activities | 67,185 | (52,653) | 46,664 |
| Financing activities | | | |
| Payments on financing lease obligations | (291) | (265) | (241) |
| Proceeds from issuance of common stock through employee benefit plans | — | 157 | 1,076 |
| Proceeds from the issuance of common stock through employee stock purchase plan | 217 | 323 | 433 |
| Proceeds from the issuance of common stock through exercise of option | 1 | — | — |
| Payment to creditor related to debt modification | (300) | — | — |
| Proceeds from issuance of common stock through at-the-market sales agreement, net of issuance costs | — | — | 11,896 |
| Proceeds from term loan, net of issuance costs | — | — | 39,619 |
| Cash and cash equivalents acquired in connection with merger, net of issuance costs paid | 11,762 | — | — |
| Proceeds from issuance of common stock and accompanying warrants and pre-funded warrants in private placement, net of issuance costs | 119,761 | — | 90,377 |
| Proceeds from issuance of common stock and warrants in public offerings, net of issuance costs | — | 70,337 | — |
| Cash paid in lieu of fractional shares due to the reverse stock split | (81) | — | — |
| Payment of issuance costs related to out of period offering | (24) | (41) | (207) |
| Net cash provided by financing activities | 131,045 | 70,511 | 142,953 |
| Net increase (decrease) in cash, cash equivalents and restricted cash | 75,165 | (81,682) | 132,253 |
| Cash, cash equivalents and restricted cash (See reconciliation in Note 6) | | | |
| Beginning of period | 95,388 | 177,070 | 44,817 |
| End of period | \$ 170,553 | \$ 95,388 | \$ 177,070 |
| Supplemental disclosure of cash flow information: | | | |
| Cash paid for interest | \$ 3,408 | \$ 3,191 | \$ 1,505 |
| Cash paid for tax | \$ — | \$ — | \$ 7 |
| Non-cash investing and financing activities: | | | |
| Property and equipment received but unpaid as of period end | \$ — | \$ 26 | \$ 6 |
| Deferred debt financing costs incurred but unpaid as of period end | \$ — | \$ 24 | \$ 5 |
| Offering costs incurred but unpaid as of period end | \$ 10 | \$ 10 | \$ 298 |

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Nature of Business

Syros Pharmaceuticals, Inc. (the "Company"), a Delaware corporation formed in November 2011, is a biopharmaceutical company committed to developing new standards of care for the frontline treatment of patients with hematologic malignancies.

The Company is subject to a number of risks similar to those of other early stage companies, including dependence on key individuals; risks inherent in the development and commercialization of medicines to treat human disease; competition from other companies, many of which are larger and better capitalized; risks relating to obtaining and maintaining necessary intellectual property protection; and the need to obtain adequate additional financing to fund the development of its product candidates and discovery activities. If the Company is unable to raise capital when needed or on favorable terms, it would be forced to delay, reduce, eliminate or out-license certain of its research and development programs or future commercialization rights to its product candidates.

On September 16, 2022, the Company filed an amendment to its Restated Certificate of Incorporation (the "Restated Certificate of Incorporation") with the Secretary of State of the State of Delaware to effect the reverse stock split of its common stock, such that every 10 shares of the Company's common stock held by a stockholder immediately prior to the reverse stock split were combined and reclassified into one share of the Company's common stock (the "Reverse Stock Split"). Except where otherwise indicated, all share and per share amounts in the accompanying financial statements, related footnotes, and management's discussion and analysis have been adjusted retroactively to reflect the Reverse Stock Split as if it had occurred at the beginning of the earliest period presented.

On September 16, 2022, the Company completed its acquisition of Tyme Technologies, Inc., a Delaware corporation ("Tyme"), in accordance with an Agreement and Plan of Merger, dated as of July 3, 2022 (the "Merger Agreement"). The Company issued approximately 7.5 million shares of its common stock to the former Tyme stockholders in exchange for all of the shares of Tyme common stock issued and outstanding immediately prior to the merger, with Tyme surviving as a wholly-owned subsidiary of the Company (the "Merger"). In connection with the closing of the Merger, and in accordance with the terms of the Merger Agreement, the Company acquired net cash, cash equivalents and marketable securities of approximately \$67.1 million.

On September 16, 2022, the Company issued in a private placement (the "2022 Private Placement") 6,387,173 shares of common stock, and, in lieu of shares of common stock, pre-funded warrants (the "2022 Pre-Funded Warrants") to purchase an aggregate of up to 7,426,739 shares of common stock, and, in each case, accompanying warrants (the "2022 Warrants") to purchase an aggregate of up to 13,813,912 additional shares of common stock (or 2022 Pre-Funded Warrants to purchase common stock in lieu thereof) at a price of \$10.34 per share and accompanying 2022 Warrant (or \$10.33 per 2022 Pre-Funded Warrant and accompanying 2022 Warrant). The 2022 Private Placement resulted in aggregate gross proceeds of \$129.9 million, before \$10.1 million of transaction costs.

In January 2021, the Company issued and sold an aggregate of 540,000 shares of common stock in an underwritten public offering at a public offering price of \$140.00 per share, resulting in gross proceeds of \$75.6 million before deducting underwriting discounts and commissions and other transaction expenses of approximately \$5.1 million.

On December 8, 2020, through a private placement, the Company issued 1,031,250 shares of common stock and, in lieu of such shares of common stock, pre-funded warrants (the "2020 Pre-Funded Warrants") to purchase an aggregate of 100,000 shares of common stock, and, in each case, accompanying warrants (the "2020 Warrants") to purchase an aggregate of up to 282,812 additional shares of common stock (or 2020 Pre-Funded Warrants to purchase common stock in lieu thereof) at a price of \$80.00 per share and accompanying 2020 Warrant (or \$79.90 per 2020 Pre-Funded Warrant and accompanying 2020 Warrant). The private placement resulted in gross proceeds of \$90.5 million, before \$0.4 million of transaction costs.

On December 4, 2020, the Company entered into an asset purchase agreement (the "Asset Purchase Agreement") with Orsenix, LLC ("Orsenix"), pursuant to which the Company acquired all of Orsenix's assets related to a novel oral form of arsenic trioxide, which the Company refers to as SY-2101 (the "Product"). Under the terms of the Asset Purchase Agreement, the Company was required to pay to Orsenix an upfront fee of \$12.0 million, which was paid in December 2020. In addition the Company is required to pay single-digit million dollar milestone payments related to

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

the development of the Product in indications other than APL; \$6.0 million following the achievement of a regulatory milestone related to the development of the Product in APL; and up to \$10.0 million upon the achievement of certain commercial milestones with respect to the Product.

The Company has incurred significant annual net operating losses in every year since its inception. It expects to continue to incur significant and increasing net operating losses for at least the next several years. The Company's net losses were \$94.7 million, \$86.6 million and \$84.0 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, the Company had an accumulated deficit of \$558.2 million. The Company has not generated any revenues from product sales, has not completed the development of any product candidate and may never have a product candidate approved for commercialization. The Company has financed its operations to date primarily through a credit facility, the sale of equity securities and through license and collaboration agreements. The Company has devoted substantially all of its financial resources and efforts to research and development and general and administrative expense to support such research and development. The Company's net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on the Company's stockholders' equity and working capital. The Company believes that its cash, cash equivalents and marketable securities of \$202.3 million as of December 31, 2022 will be sufficient to allow the Company to fund its current operating plan for a period of at least 12 months past the issuance date of these consolidated financial statements.

2. Summary of Significant Accounting Policies

Basis of Presentation

The Company's consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States ("U.S. GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative U.S. GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, (i) Syros Securities Corporation, a Massachusetts corporation formed by the Company in December 2014 to exclusively engage in buying, selling and holding securities on its own behalf, (ii) Syros Pharmaceuticals (Ireland) Limited, an Irish limited liability company formed by the Company in January 2019, and (iii) Tyme Technologies, Inc., a Delaware corporation, which is the surviving corporation in connection with the filing of a certificate of merger with the Secretary of State of the State of Delaware on September 16, 2022, pursuant to which Tack Acquisition Corp., a Delaware corporation formed by the Company in June 2022 to effect the Merger, merged with and into Tyme Technologies, Inc. (refer to Note 1). All intercompany transactions and balances have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts in the financial statements and accompanying notes. Management considers many factors in selecting appropriate financial accounting policies and in developing the estimates and assumptions that are used in the preparation of the financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, which include, but are not limited to, expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates and whether historical trends are expected to be representative of future trends. Management's estimation process often may yield a range of potentially reasonable estimates and management must select an amount that falls within that range of reasonable estimates. On an ongoing basis, the Company's management evaluates its estimates, which include, but are not limited to, estimates related to revenue recognition, warrant liabilities, stock-based compensation expense, accrued expenses, income taxes and the evaluation of the existence of conditions and events that raise substantial doubt regarding the Company's ability to continue as a going concern. Actual results may differ from those estimates or assumptions.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

Segment Information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision-making group, in making decisions on how to allocate resources and assess performance. The Company's chief operating decision maker is the Chief Executive Officer. The Company and the chief operating decision maker view the Company's operations and manage its business in one operating segment. The Company operates only in the United States.

Cash and Cash Equivalents

The Company considers all highly liquid instruments that have original maturities of three months or less when acquired to be cash equivalents. Cash equivalents, which consist of money market funds that invest in U.S. Treasury obligations, as well as overnight repurchase agreements, are stated at fair value. The Company maintains its bank accounts at one major financial institution.

Off-Balance Sheet Risk and Concentrations of Credit Risk

The Company has no financial instruments with off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially subject the Company to concentrations of credit risk primarily consist of cash equivalents and marketable securities. Under its investment policy, the Company limits amounts invested in such securities by credit rating, maturity, industry group, investment type and issuer, except for securities issued by the U.S. government. The Company is not exposed to any significant concentrations of credit risk from these financial instruments. The goals of the Company's investment policy, in order of priority, are safety and preservation of principal and liquidity of investments sufficient to meet cash flow requirements.

Fair Value of Financial Instruments

ASC 820, *Fair Value Measurement* ("ASC 820"), established a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumption about the inputs that market participants would use in pricing the asset or liability. These are developed based on the best information available under the circumstances.

ASC 820 identified fair value as the exchange price, or exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As a basis for considering market participant assumptions in fair value measurements, ASC 820 established a three-tier fair value hierarchy that distinguishes between the following:

Level 1—Quoted market prices (unadjusted) in active markets for identical assets or liabilities.

Level 2—Inputs other than quoted prices included within Level 1 that are either directly or indirectly observable, such as quoted market prices, interest rates and yield curves.

Level 3—Unobservable inputs developed using estimates or assumptions developed by the Company, which reflect those that a market participant would use.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized as Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reflected in the consolidated balance sheets for cash and cash equivalents, prepaid expenses, other current assets, restricted cash, accounts payable, accrued expenses, and deferred revenue approximate their respective fair values due to their short-term nature.

Property and Equipment

Property and equipment consists of laboratory equipment, computer equipment, furniture and fixtures and leasehold improvements, all of which are stated at cost, less accumulated depreciation. Expenditures for maintenance and repairs that do not improve or extend the lives of the respective assets are recorded to expense as incurred. Major betterments are capitalized as additions to property and equipment. Depreciation and amortization are recognized over the estimated useful lives of the assets using the straight-line method.

Construction-in-progress is stated at cost, which relates to the cost of leasehold improvements not yet placed into service. No depreciation expense is recorded on construction-in-progress until such time as the relevant assets are completed and put into use.

Impairment of Long-Lived Assets

The Company continually evaluates long-lived assets for potential impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparing the book values of the assets to the expected future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book values of the assets exceed their fair value. The Company has not recognized any impairment losses from inception through December 31, 2022.

Other Long-Term Assets

As of December 31, 2022 and 2021, other long-term assets primarily consisted of advance payments made to the contract research organizations responsible for conducting the Company's tamibarotene and SY-5609 clinical trials.

Revenue Recognition

To date the Company's only revenue has consisted of collaboration and license revenue. The Company has not generated any revenue from product sales and does not expect to generate any revenue from product sales for the foreseeable future.

The Company recognizes revenue in accordance with ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps:

- (i) identify the contract(s) with a customer;
- (ii) identify the performance obligations in the contract;
- (iii) determine the transaction price;
- (iv) allocate the transaction price to the performance obligations in the contract; and
- (v) recognize revenue when (or as) the entity satisfies a performance obligation.

The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. If a contract is determined to be within the scope of ASC 606 at inception, the Company assesses the goods or services promised within such contract, determines which of those goods and services are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

If the Company performs by transferring goods or services to a customer before the customer pays consideration or before payment is due, the Company records a contract asset, excluding any amounts presented as accounts receivable. The Company includes contract assets as unbilled accounts receivable on its consolidated balance sheets. The Company records accounts receivable for amounts billed to the customer for which the Company has an unconditional right to consideration. The Company assesses contract assets and accounts receivable for impairment and, to date, no impairment losses have been recorded.

From time to time, the Company may enter into agreements that are within the scope of ASC 606. The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, up-front license fees or prepaid research and development services; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products. Each of these payments results in license and collaboration revenues, except for revenues from royalties on net sales of licensed products, which will be classified as royalty revenues.

The Company analyzes its collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808"), to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to ASC 606. For those elements of the arrangement that are accounted for pursuant to ASC 606, the Company applies the five-step model described above.

Research and Development

Expenditures relating to research and development are expensed in the period incurred. Research and development expenses consist of both internal and external costs associated with the development of the Company's gene control platform and product candidates. Research and development costs include salaries and benefits, materials and supplies, external research, preclinical and clinical development expenses, stock-based compensation expense and facilities costs. Facilities costs primarily include the allocation of rent, utilities, depreciation and amortization.

In certain circumstances, the Company is required to make nonrefundable advance payments to vendors for goods or services that will be received in the future for use in research and development activities. In such circumstances, the nonrefundable advance payments are deferred and capitalized, even when there is no alternative future use for the research and development, until related goods or services are provided.

The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the work being performed, including the phase or completion of the event, invoices received and costs. Significant judgements and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates.

The Company may in-license the rights to develop and commercialize product candidates. For each in-license transaction the Company evaluates whether it has acquired processes or activities along with inputs that would be sufficient to constitute a "business" as defined under U.S. GAAP. A "business" as defined under U.S. GAAP consists of inputs and processes applied to those inputs that have the ability to create outputs. Although businesses usually have outputs, outputs are not required for an integrated set of activities to qualify as a business. When the Company determines that it has not acquired sufficient processes or activities to constitute a business, any up-front payments, as well as milestone payments, are immediately expensed as acquired research and development in the period in which they are incurred.

Warrants

The Company accounts for issued warrants as either liability or equity in accordance with ASC 480-10, *Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity* (“ASC 480-10”) or ASC 815-40, *Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company’s Own Stock* (“ASC 815-40”). Under ASC 480-10, warrants are considered liabilities if they are mandatorily redeemable and they require settlement in cash or other assets, or a variable number of shares. If warrants do not meet liability classification under ASC 480-10, the Company considers the requirements of ASC 815-40 to determine whether the warrants should be classified as liability or equity. Under ASC 815-40, contracts that may require settlement for cash are liabilities, regardless of the probability of the occurrence of the triggering event. Liability classified warrants are measured at fair value on the issuance date and at the end of each reporting period. Any change in the fair value of the warrants after the issuance date is recorded in the consolidated statements of operations as a gain or loss. If warrants do not require liability classification under ASC 815-40, in order to conclude warrants should be classified as equity, the Company assesses whether the warrants are indexed to its common stock and whether the warrants are classified as equity under ASC 815-40 or other applicable GAAP. Equity classified warrants are accounted for at fair value on the issuance date with no changes in fair value recognized after the issuance date.

Stock-Based Compensation Expense

The Company accounts for its stock-based compensation awards in accordance with ASC 718, *Compensation—Stock Compensation* (“ASC 718”). ASC 718 requires all stock-based payments to employees and directors, including grants of restricted stock units and stock option awards, to be recognized as expense in the consolidated statements of operations based on their grant date fair values. The Company estimates the fair value of stock options granted using the Black-Scholes option-pricing model. Prior to June 30, 2016, the Company was a private company and, therefore, lacks Company-specific historical and implied volatility information. As a result, the Company estimates its expected stock volatility based on a combination of its historical volatility and that of a publicly traded set of peer companies. The expected term of the Company’s stock options granted to employees has been determined utilizing the “simplified” method for awards that qualify as “plain-vanilla” options. The Company uses the contractual term in determining the expected term of the stock options granted to non-employees. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future. The Company uses the value of its common stock at the grant date to determine the fair value of restricted stock awards.

The Company expenses the fair value of its stock-based awards to employees and non-employees on a straight-line basis over the associated service period, which is generally the vesting period. The Company accounts for forfeitures as they occur instead of estimating forfeitures at the time of grant. Ultimately, the actual expense recognized over the vesting period will be for only those options that vest.

Compensation expense for discounted purchases under the employee stock purchase plan is measured using the Black-Scholes model to compute the fair value of the lookback provision plus the purchase discount and is recognized as compensation expense over the offering period.

For stock-based awards that contain performance-based milestones, the Company records stock-based compensation expense in accordance with the accelerated attribution model. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. For certain of the performance-based awards, notwithstanding any vesting in accordance with the achievement of performance-based milestones, such awards vest in full on the sixth anniversary of the vesting commencement date. Compensation expense for such awards is recognized over the six-year vesting period unless management determines that the achievement of any performance-based milestones is probable, in which case expense is accelerated. Compensation expense related to these awards were all recognized as of December 31, 2020 as the performance-based milestones were achieved.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

Income Taxes

The Company accounts for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position.

Net Loss per Share

Basic net earnings per share applicable to common stockholders is calculated by dividing net earnings applicable to common stockholders by the weighted average shares outstanding during the period, without consideration for common stock equivalents. Diluted net earnings per share applicable to common stockholders is calculated by adjusting the weighted average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury-stock method and the if-converted method. For purposes of the calculation of diluted net loss per share applicable to common stockholders, stock options, unvested restricted stock units, and warrants are considered to be common stock equivalents but are excluded from the calculation of diluted net loss per share applicable to common stockholders, as their effect would be anti-dilutive; therefore, basic and diluted net loss per share applicable to common stockholders were the same for all periods presented.

As of December 31, 2022 and 2021, 100,000 2020 Pre-Funded Warrants to purchase common stock, issued in connection with the December 2020 private placement, and 7,426,739 2022 Pre-Funded Warrants issued in connection with the September 2022 Private Placement (refer to Note 12), were included in the basic and diluted net loss per share calculation.

The following common stock equivalents were excluded from the calculation of diluted net loss per share applicable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

| | As of December 31, | | |
|---------------------------------|--------------------|------------------|------------------|
| | 2022 | 2021 | 2020 |
| Stock options | 1,727,327 | 665,727 | 546,861 |
| Unvested restricted stock units | 1,204,421 | 268,749 | 173,438 |
| Warrants* | 14,142,298 | 499,016 | 499,016 |
| Total | 17,074,046 | 1,433,492 | 1,219,315 |

* As of December 31, 2022, this is comprised of 2,754 warrants to purchase common stock issued in connection with the execution and first draw of the Loan Agreement in February 2020 (refer to Note 8), 1,738 warrants to purchase common stock issued in connection with the second draw on the Loan Agreement in December 2020 (refer to Note 8), 282,809 warrants to purchase common stock issued in connection with the private placement in December 2020 (refer to Note 12), 13,813,912 warrants to purchase common stock issued in connection with the private placement in September 2022 (refer to Note 12), and 41,085 warrants to purchase common stock that were issued upon the assumption and conversion of Tyme warrants in connection with the Merger (refer to Note 3). As of December 31, 2021 and 2020, this is comprised of 211,709 warrants to purchase common stock issued in connection with the Company's April 2019 financing (refer to Note 12), 2,755 warrants to purchase common stock issued in connection with the execution and first draw of the Loan Agreement in February 2020 (refer to Note 8), 1,739 warrants to purchase common stock issued in connection with the second draw on the Loan Agreement in December 2020 (refer to Note 8), and 282,813 warrants to purchase common stock issued in connection with the private placement in December 2020 (refer to Note 12).

The weighted average number of common shares used in net loss per share applicable to common stockholders on a basic and diluted basis were 12,631,968, 6,253,498 and 4,605,162 shares for the years ended December 31, 2022, 2021 and 2020, respectively.

Recent Accounting Pronouncements

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* (“ASU 2016-13”), which requires the measurement and recognition of expected credit losses for financial assets held at amortized cost. ASU 2016-13 replaces the existing incurred loss impairment model with an expected loss model that requires the use of forward-looking information to calculate credit loss estimates. It also eliminates the concept of other-than-temporary impairment and requires credit losses on available-for-sale debt securities to be recorded through an allowance for credit losses instead of as a reduction in the amortized cost basis of the securities. As a smaller reporting company, ASU 2016-13 will become effective for the Company for fiscal years beginning after December 15, 2022, and early adoption is permitted. The Company is currently evaluating this new standard and does not anticipate that it will have a material impact on its consolidated financial statements and related disclosures.

Recently Adopted Accounting Pronouncements

In August 2020, the FASB issued ASU No. 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity’s Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity* (“ASU 2020-06”). The amendments in ASU 2020-06 simplify the accounting for certain financial instruments with characteristics of liabilities and equity, including convertible instruments and contracts in an entity’s own equity. The standard is effective for public companies for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2021. The Company has adopted on a modified retrospective basis the new standard effective January 1, 2022, and it did not have a material impact on its consolidated financial statements and related disclosures.

3. Recapitalization

On September 16, 2022, the Company issued approximately 7.5 million shares of its common stock to the former Tyme stockholders in connection with the Merger. The Company also issued options and warrants to purchase 733,545 shares of the Company’s common stock to certain holders of Tyme options and warrants that were outstanding immediately before the consummation of the Merger. The Merger is accounted for as a recapitalization because the Company was determined to be a legal and accounting acquirer under Financial Accounting Standards Board’s Accounting Standards Codification Topic 805, Business Combinations (“ASC 805”). This determination was primarily based on the following facts and circumstances:

- The pre-combination equity holders of the Company hold the relative majority of voting rights in the combined entity;
- The pre-combination equity holders of the Company have the right to appoint the majority of the directors on the combined entity’s board of directors;
- Senior management of the Company comprises the senior management of the combined entity;
- Operations of the Company comprise the ongoing operations of the combined entity; and
- Upon effectiveness of the Merger, the primary assets of Tyme at the effective date were primarily cash, cash equivalents and marketable securities.

Under the recapitalization accounting model, the net assets acquired are recognized at fair value and any excess consideration transferred over the fair value of the net assets are reflected as a reduction to equity. Transaction costs incurred attributable to the Merger are also reflected as a reduction to the equity.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

The carrying value of Tyme's net assets as of September 16, 2022, which approximates fair value because of its short-term nature, is set forth below:

| | Fair Value |
|---------------------------|------------|
| Cash and cash equivalents | \$ 14,898 |
| Marketable securities | 52,220 |
| Prepaid expenses | 1,350 |
| Total | \$ 68,468 |

No value has been ascribed to the development programs acquired from Tyme in the Merger.

The Company incurred \$3.1 million of transaction costs attributable to the Merger which are reflected as a reduction of additional paid-in capital. In addition, the Company paid \$4.5 million of severance to former Tyme employees which is included in the Company's statement of operations as transaction related expenses.

4. Collaboration and Research Arrangements

Collaboration with Global Blood Therapeutics

On December 17, 2019, the Company entered into a license and collaboration agreement (the "GBT Collaboration Agreement") with GBT, pursuant to which the parties agreed to a research collaboration to discover novel targets that induce fetal hemoglobin in order to develop new small molecule treatments for sickle cell disease and beta thalassemia. The research term (the "Research Term") is for an initial period of three years and can be extended for up to two (2) additional one-year terms upon mutual agreement. In November 2022, the Company and GBT agreed to extend the Research Term for an additional one-year period, with the Research Term now scheduled to end in December 2023.

Pursuant to the terms of the GBT Collaboration Agreement, GBT agreed to pay the Company an upfront payment of \$20.0 million, which was collected in January 2020. GBT also agreed to reimburse the Company for full-time employee and out-of-pocket costs and expenses incurred by the Company in accordance with the agreed-upon research budget, which was anticipated to total approximately \$40.0 million over the initial Research Term.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

The Company granted to GBT an option (the “Option”) to obtain an exclusive, worldwide license, with the right to sublicense, under relevant intellectual property rights and know-how of the Company arising from the collaboration to develop, manufacture and commercialize any compounds or products resulting from the collaboration. GBT may exercise the Option at any time during the period (i) commencing on the earlier of (a) the date of GBT’s designation of the first product candidate to enter into investigational new drug application-enabling studies, or (b) if no such candidate is designated as of the expiration of the Research Term, the date of expiration of the Research Term, and (ii) ending on the 180th day after the date of expiration or earlier termination of the Research Term. GBT’s exercise of the Option will be subject to any required filings with the applicable antitrust authority as required by the antitrust laws and satisfaction of any applicable antitrust conditions.

Should GBT exercise its Option, the Company could receive up to \$315.0 million in option exercise, development, regulatory, commercialization and sales-based milestones per product candidate and product resulting from the collaboration.

The Company will also be entitled to receive, subject to certain reductions, tiered mid-to-high single digit royalties as percentages of calendar year net sales on any product.

Either party may terminate the GBT Collaboration Agreement for the other party’s uncured material breach or insolvency, and in certain other specified circumstances, subject to specified notice and cure periods. GBT may unilaterally terminate the GBT Collaboration Agreement in its entirety, for any or no reason, upon nine-months’ prior written notice to the Company if such notice is delivered during the Research Term, or 90 days’ prior written notice to the Company if such notice is delivered after the expiration or termination of the Research Term.

GBT Collaboration Revenue

The Company analyzed the GBT Collaboration Agreement and concluded that it represents a contract with a customer within the scope of ASC 606.

The Company has identified a single performance obligation, which includes a (i) non-exclusive research license that GBT will have access to during the initial Research Term and (ii) research and development services provided during the initial Research Term. The GBT Collaboration Agreement includes the Option. The Option does not provide a material right to GBT that it would receive without entering into the GBT Collaboration Agreement, principally because the Option exercise fee is at least equal to the standalone selling price for the underlying goods. The non-exclusive research license is not distinct as GBT cannot benefit from the license without the research and development services that are separately identifiable in the contract. The non-exclusive research license only allows GBT to evaluate the candidate compounds developed under the research plan or to conduct work allocated to it during the Research Term. GBT cannot extract any benefit from the non-exclusive research license without the research and development services performed by the Company, including the provision of data package information. As such, these two promises are inputs to a combined output (the delivery of data package allowing GBT to make an Option exercise decision) and are bundled into a single performance obligation (the non-exclusive research license and research and development service performance obligation).

At inception, the total transaction price was determined to be approximately \$60.0 million, which consisted of a \$20.0 million upfront non-refundable and non-creditable technology access fee and approximately \$40.0 million in reimbursable costs for employee and external research and development expenses. The GBT Collaboration Agreement also provides for development and regulatory milestones which are only payable subsequent to the exercise of the Option, and therefore are excluded from transaction price at inception. The Company will re-evaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur. As of December 31, 2022, the transaction price is estimated at \$56.4 million, which reflects a reduction in the initial estimated transaction price from \$60.0 million to \$49.2 million based on a lower reimbursable cost incurred, offset by additional consideration of \$7.1 million related to the one year extension of the Research Term. The Company accounted for the contract amendment as a modification as if it were part of the existing contract as the remaining goods and services are not distinct, and therefore form part of a single performance obligation that was partially satisfied at the date of the amendment.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

ASC 606 requires an entity to recognize revenue only when it satisfies a performance obligation by transferring a promised good or service to a customer. A good or service is considered to be transferred when the customer obtains control. As the non-exclusive research license and research and development services represent one performance obligation, the Company has determined that it will satisfy its performance obligation over a period of time as services are performed and GBT receives the benefit of the services, as the overall purpose of the arrangement is for the Company to perform the services. The Company will recognize revenue associated with the performance obligation as the research and development services are provided using an input method, according to the costs incurred as related to the research and development activities and the costs expected to be incurred in the future to satisfy the performance obligation. The transfer of control occurs during this time and is the best measure of progress towards satisfying the performance obligation.

The Company had no account receivable balance as of December 31, 2022 and 2021. The Company had contract asset balances of \$1.7 million and \$3.0 million as of December 31, 2022 and 2021, respectively. As of December 31, 2022, the Company had deferred revenue related to the GBT Collaboration Agreement of \$4.3 million, all of which was classified as deferred revenue, current portion on the Company's consolidated balance sheet. As of December 31, 2021, the Company had deferred revenue of \$9.0 million, all of which was classified as deferred revenue, current portion on the Company's consolidated balance sheet. The extension of the Research Term has changed our estimate of the total effort to satisfy the performance obligation, as a result we recorded a cumulative catch up adjustment of \$0.8 million decrease in revenue during the fourth quarter of 2022. The Company recognized revenue under the GBT Collaboration Agreement of \$13.6 million, \$19.4 million and \$11.7 million during the years ended December 31, 2022, 2021, and 2020, respectively.

Agreements with Incyte Corporation

In January 2018, the Company and Incyte entered into a Target Discovery, Research Collaboration and Option Agreement (the "Incyte Collaboration Agreement"). The Incyte Collaboration Agreement was amended in November 2019. Under the Incyte Collaboration Agreement, the Company is using its proprietary gene control platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte has received options to obtain exclusive worldwide rights to intellectual property resulting from the collaboration for the development and commercialization of therapeutic products directed to up to seven validated targets. For each option exercised by Incyte, Incyte will have the exclusive worldwide right to use the licensed intellectual property to develop and commercialize therapeutic products that modulate the target as to which the option was exercised. Under the terms of the Incyte Collaboration Agreement, Incyte paid the Company \$10.0 million in up-front consideration, consisting of \$2.5 million in cash and \$7.5 million in pre-paid research funding (the "Prepaid Research Amount"). The Company's activities under the Incyte Collaboration Agreement are subject to a joint research plan and, subject to certain exceptions, Incyte is responsible for funding the Company's activities under the research plan, including amounts in excess of the Prepaid Research Amount. As of December 31, 2022, the Company has completed all of the target validation activities allocated to it under the research plan.

In January 2018, the Company also entered into a Stock Purchase Agreement with Incyte (the "Stock Purchase Agreement") whereby, for an aggregate purchase price of \$10.0 million, Incyte purchased 79,302 shares of the Company's common stock at \$126.10 per share. Under the terms of the Stock Purchase Agreement, the shares were purchased at a 30% premium over the volume-weighted sale price of the shares of the Company's common stock over the 15-trading day period immediately preceding the date of the Stock Purchase Agreement.

Incyte Collaboration Revenue

The Company analyzed the Incyte Collaboration Agreement and concluded that it represents a contract with a customer within the scope of ASC 606.

The Company identified a single performance obligation which includes (i) a research license that Incyte retains as long as there remains an unexercised option (the "Research License") and (ii) research and development services provided during the research term. The Incyte Collaboration Agreement includes options to (x) obtain additional time to exercise the license options for certain targets designated as definitive validation targets and (y) obtain license rights to each validated target, both of which were not considered by the Company's management to be material rights, and therefore not performance obligations, at inception.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

At inception, the total transaction price was determined to be \$12.3 million. Following a November 2019 amendment, the total transaction price is now \$12.8 million, consisting of a \$2.5 million upfront non-refundable and non-creditable payment, the \$7.5 million Prepaid Research Amount and \$2.3 million in premium paid on the equity investment made pursuant the Stock Purchase Agreement and \$0.5 million of additional consideration. The Company accounted for the contract amendment as a modification as if it were part of the existing contract as the remaining goods and services are not distinct, and therefore form part of a single performance obligation that was partially satisfied at the date of the amendment.

The Incyte Collaboration Agreement also provides for development and regulatory milestones that are only payable subsequent to the exercise of an option and were therefore excluded from transaction price at inception. The Company re-evaluates the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur.

The Company recognizes revenue associated with the performance obligation as the research and development services are provided using an input method, according to the costs incurred as related to the research and development activities and the costs expected to be incurred in the future to satisfy the performance obligation. The transfer of control occurs during this time and is the best measure of progress towards satisfying the performance obligation.

During the years ended December 31, 2022, 2021 and 2020, the Company recognized \$1.3 million, \$4.1 million and \$3.4 million of revenue, respectively, under the Incyte Collaboration Agreement. As of December 31, 2022, the Company has no deferred revenue outstanding under the Incyte Collaboration Agreement.

The following table presents the changes in contract assets and liabilities for the year ended December 31, 2022 (in thousands):

| | Balance at December 31, 2021 | Additions | Deductions | Balance at December 31, 2022 |
|--|---------------------------------|------------------|---------------------|------------------------------------|
| Accounts receivable and contract assets: | | | | |
| Billed receivables from collaboration partners | \$ — | \$ 10,315 | \$ (10,315) | \$ — |
| Unbilled receivables from collaboration partners | 2,979 | 9,169 | (10,454) | 1,694 |
| Total accounts receivable and contract assets | <u>\$ 2,979</u> | <u>\$ 19,484</u> | <u>\$ (20,769)</u> | <u>\$ 1,694</u> |
| Contract liabilities: | | | | |
| Deferred revenue - Incyte | \$ 1,268 | \$ — | \$ (1,268) | \$ — |
| Deferred revenue - GBT | 8,913 | 2,944 | (7,527) | 4,330 |
| Total contract liabilities | <u>\$ 10,181</u> | <u>\$ 2,944</u> | <u>\$ (8,795)</u> | <u>\$ 4,330</u> |

The changes in deferred revenue are due to the timing of the payments, the recognition of revenue and the cumulative catch up adjustment related to the Company's collaboration agreements during the period.

5. Cash, Cash Equivalents and Marketable Securities

Cash equivalents are highly liquid investments that are readily convertible into cash with original maturities of three months or less when purchased. Marketable securities consist of securities with original maturities greater than 90 days when purchased. The Company classifies these marketable securities as available-for-sale and records them at fair value in the accompanying consolidated balance sheets. Unrealized gains or losses are included in accumulated other comprehensive loss. Premiums or discounts from par value are amortized to other income over the life of the underlying security.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

Cash, cash equivalents and marketable securities, available-for-sale, consisted of the following at December 31, 2022 and December 31, 2021 (in thousands):

| December 31, 2022 | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|---|-----------------------|-------------------------|--------------------------|-------------------|
| Cash and cash equivalents: | | | | |
| Cash and money market funds | \$ 167,467 | | \$ — | \$ 167,467 |
| Marketable securities: | | | | |
| Corporate debt securities - due in one year or less | 22,257 | 116 | (53) | 22,320 |
| Commercial paper | 2,491 | — | — | 2,491 |
| Municipal bonds | 5,987 | 51 | — | 6,038 |
| US Treasury obligation - due in one year or less | 4,000 | | (12) | 3,988 |
| Total | \$ 202,202 | \$ 167 | \$ (65) | \$ 202,304 |

| December 31, 2021 | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|---|-----------------------|-------------------------|--------------------------|-------------------|
| Cash and cash equivalents: | | | | |
| Cash and money market funds | \$ 92,302 | \$ — | \$ — | \$ 92,302 |
| Marketable securities: | | | | |
| Corporate debt securities - due in one year or less | 30,100 | — | (12) | 30,088 |
| US Treasury obligation - due in one year or less | 8,000 | — | (21) | 7,979 |
| Corporate debt securities - due in more than one year to five years | 9,085 | — | (33) | 9,052 |
| US Treasury obligation - due in more than one year to five years | 3,999 | — | (13) | 3,986 |
| Total | \$ 143,486 | \$ — | \$ (79) | \$ 143,407 |

Although available to be sold to meet operating needs or otherwise, securities are generally held through maturity. The cost of securities sold is determined based on the specific identification method for purposes of recording realized gains and losses. During the years ended December 31, 2022, 2021 and 2020, there were no realized gains or losses on sales of investments, and no investments were adjusted for other than temporary declines in fair value.

As of December 31, 2022 and December 31, 2021, marketable securities with maturities of one year or less when purchased are presented in current assets and those with maturities of more than one year are presented in the noncurrent assets in the accompanying consolidated balance sheet.

As of December 31, 2022, the Company held five securities that were in an unrealized loss position. The aggregate fair value of securities held by the Company in an unrealized loss position for less than 12 months as of December 31, 2022 was \$12.9 million. There were no securities held by the Company in an unrealized loss position for more than 12 months as of December 31, 2022. The Company has the intent and ability to hold such securities until recovery. The Company determined that there was no material change in the credit risk of the above marketable securities during the year ended December 31, 2022. As a result, the Company determined it did not hold any marketable securities with an other than temporary impairment as of December 31, 2022.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

6. Fair Value Measurements

Assets and liabilities measured at fair value on a recurring basis as of December 31, 2022 and 2021 were as follows (in thousands):

| Description | December 31, 2022 | Active Markets (Level 1) | Observable Inputs (Level 2) | Unobservable Inputs (Level 3) |
|---|-------------------|--------------------------------|-----------------------------------|-------------------------------------|
| Assets: | | | | |
| Cash | \$ 167,467 | \$ 167,467 | — | — |
| Corporate debt securities - due in one year or less | 22,320 | — | 22,320 | — |
| Commercial paper | 2,491 | — | 2,491 | — |
| Municipal bonds | 6,038 | — | 6,038 | — |
| US Treasury obligation - due in one year or less | 3,988 | 3,988 | — | — |
| Total | <u>\$ 202,304</u> | <u>\$ 171,455</u> | <u>\$ 30,849</u> | <u>\$ —</u> |
| Liabilities: | | | | |
| Warrant liabilities | \$ 24,472 | \$ — | \$ — | \$ 24,472 |
| Total | <u>\$ 24,472</u> | <u>\$ —</u> | <u>\$ —</u> | <u>\$ 24,472</u> |

| Description | December 31, 2021 | Active Markets (Level 1) | Observable Inputs (Level 2) | Unobservable Inputs (Level 3) |
|---|-------------------|--------------------------------|-----------------------------------|-------------------------------------|
| Assets: | | | | |
| Cash | \$ 57,213 | \$ 57,213 | \$ — | \$ — |
| Money market funds | 35,089 | 35,089 | — | — |
| Corporate debt securities - due in one year or less | 30,088 | — | 30,088 | — |
| US Treasury obligation - due in one year or less | 7,979 | 7,979 | — | — |
| US Treasury obligation - due in more than one year to five years | 3,986 | 3,986 | — | — |
| Corporate debt securities - due in more than one year to five years | 9,052 | — | 9,052 | — |
| Total | <u>\$ 143,407</u> | <u>\$ 104,267</u> | <u>\$ 39,140</u> | <u>\$ —</u> |
| Liabilities: | | | | |
| Warrant liabilities | \$ 3,029 | \$ — | \$ — | \$ 3,029 |
| Total | <u>\$ 3,029</u> | <u>\$ —</u> | <u>\$ —</u> | <u>\$ 3,029</u> |

Assumptions Used in Determining Fair Value of Warrants

The Company issued the 2022 Warrants to purchase an aggregate of up to 13,813,912 shares of common stock in connection with the 2022 Private Placement (see Note 12) and the 2020 Warrants to purchase an aggregate of up to 282,809 shares of common stock in connection with a private placement in December 2020 (see Note 12). The Company accounted for the 2022 Warrants and 2020 Warrants as liabilities. The Company recorded the fair value of these warrants upon issuance using the Black-Scholes valuation model and is required to revalue these warrants at each reporting date with any changes in fair value recorded on our statement of operations. The valuation of the 2022 Warrants and 2020 Warrants is considered under Level 3 of the fair value hierarchy and influenced by the fair value of the underlying common stock of the Company.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

A summary of the Black Scholes pricing model assumptions used to record the fair value of the warrants is as follows:

| | December 31, 2022 | | December 31, 2021 |
|----------------------------------|-------------------|----|-------------------|
| Stock price | \$ 3.59 | \$ | 3.26 |
| Average risk-free interest rate | 4.02 % | % | 1.11 % |
| Dividend yield | — | | — |
| Average expected life (in years) | 4.67 | | 3.94 |
| Average expected volatility | 86.79 % | % | 81.14 % |

Changes in Level 3 Liabilities Measured at Fair Value on a Recurring Basis

The following table reflects the change in the Company's Level 3 Warrant liabilities for the years ended December 31, 2022 and 2021 (in thousands):

| | December 31, 2022 | | December 31, 2021 |
|---|-------------------|----|-------------------|
| Fair value of warrant liabilities as of beginning of year | \$ 3,029 | \$ | 19,711 |
| Warrants issued in connection with 2022 Private Placement | 64,664 | | — |
| Change in fair value | (43,221) | | (16,682) |
| Fair value of warrant liabilities as of end of year | \$ 24,472 | \$ | 3,029 |

7. Restricted Cash

As of December 31, 2022 and 2021, the Company had \$3.1 million in restricted cash, which was classified as long-term on the Company's condensed consolidated balance sheets, and all of which was attributable to the HQ Lease (See Note 9).

In connection with the execution of the HQ Lease, the Company was required to provide the landlord with a letter of credit in the amount of \$3.1 million that will expire 95 days after expiration or early termination of the HQ Lease. The Company will have the right, under certain conditions, to reduce the amount of the letter of credit to \$2.1 million in October 2023.

The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the consolidated balance sheets that sum to the total of the amounts shown in the consolidated statement of cash flows as of December 31, 2022, 2021, and 2020 (in thousands):

| | 2022 | December 31, 2021 | 2020 |
|--|-------------------|----------------------|-------------------|
| Cash and cash equivalents | \$ 167,467 | \$ 92,302 | \$ 173,984 |
| Restricted cash, net of current portion | \$ 3,086 | 3,086 | 3,086 |
| Total cash, cash equivalents and restricted cash | <u>\$ 170,553</u> | <u>\$ 95,388</u> | <u>\$ 177,070</u> |

8. Oxford Finance Loan Agreement

On February 12, 2020, the Company entered into a Loan and Security Agreement (the "Loan Agreement") with Oxford Finance LLC (the "Lender"). Pursuant to the Loan Agreement, a term loan of up to an aggregate principal amount of \$60.0 million is available to the Company. A \$20.0 million term loan (first tranche) was funded on February 12, 2020, and another \$20.0 million term loan (second tranche) was funded on December 23, 2020. As of December 31, 2022, the final \$20.0 million tranche remained available under the Loan Agreement, at the sole discretion of the Lender.

The term loan initially bore interest at an annual rate equal to the greater of (i) 7.75% and (ii) the sum of 5.98% and the greater of (A) one-month LIBOR or (B) 1.77%. The Loan Agreement initially provided for interest-only

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

payments until March 1, 2023, and repayment of the aggregate outstanding principal balance of the term loan in monthly installments starting on March 1, 2023 and continuing through February 1, 2025 (the "Maturity Date"). Pursuant to the terms of an amendment to the Loan Agreement dated July 3, 2022 (the "Loan Agreement Amendment"), effective September 16, 2022, Oxford agreed to extend the interest-only period from March 1, 2023 to March 1, 2024 and to extend the Maturity Date from February 1, 2025 to February 1, 2026, and upon the achievement of certain milestones and subject to the payment of certain fees, further extend the interest only period to September 1, 2024 and the Maturity Date to August 1, 2026. Pursuant to the terms of a subsequent amendment to the Loan Agreement dated November 15, 2022, the floating annual rate for each term loan was amended to equal the greater of (i) 7.75% and (ii) the sum of (a) the 1-month CME Term SOFR reference rate, (b) 0.10%, and (c) 5.98%.

The Company paid a facility fee of \$0.1 million upon the issuance of the first tranche, paid a facility fee of \$75,000 upon the issuance of the second tranche, and must pay a \$50,000 facility fee if and when the third tranche is issued. The Company also paid fees of \$300,000 related to the Loan Agreement Amendment. The Company is required to make a final payment equal to 5.00% of the amount of the term loan drawn payable on the earlier of (i) the prepayment of the term loan or (ii) the Maturity Date. At the Company's option, the Company may elect to prepay the loans subject to a prepayment fee equal to the following percentage of the principal amount being prepaid: 2% if an advance is prepaid during the first 12 months following the applicable advance date, 1% if an advance is prepaid after 12 months but prior to 24 months following the applicable advance date, and 0.5% if an advance is prepaid any time after 24 months following the applicable advance date but prior to the Maturity Date.

In connection with the Loan Agreement, the Company granted the Lender a security interest in all of the Company's personal property now owned or hereafter acquired, excluding intellectual property (but including the right to payments and proceeds of intellectual property), and a negative pledge on intellectual property. The Loan Agreement also contains certain events of default, representations, warranties and non-financial covenants of the Company.

In connection with the issuance of the first tranche, the Company issued the Lender warrants to purchase 2,754 shares of the Company's common stock at an exercise price per share of \$72.60 in February 2020. In connection with the issuance of the second tranche, the Company issued the Lender warrants to purchase 1,738 shares of the Company's common stock at an exercise price of \$115.00 per share in December 2020 (collectively, the "Oxford Warrants"). The Oxford Warrants are exercisable within five years from the respective dates of issuance.

The Oxford Warrants are classified as a component of permanent equity because they are freestanding financial instruments that are legally detachable and separately exercisable from the shares of common stock with which they were issued, are immediately exercisable, do not embody an obligation for the Company to repurchase its shares, and permit the holders to receive a fixed number of shares of common stock upon exercise. In addition, the Oxford Warrants do not provide any guarantee of value or return. The Company valued the Oxford Warrants at issuance using the Black-Scholes option pricing model and determined the fair value of the Oxford Warrants to be \$0.1 million for the first tranche and \$0.2 million for the second tranche. The key inputs to the valuation model included an average volatility of 75.43% for the first tranche and 82.41% for the second tranche, and an expected term of 5.0 years for both tranches.

The Company has the following minimum aggregate future loan payments as of December 31, 2022 (in thousands):

| | |
|--|------------------|
| Year ending December 31, 2023 | \$ — |
| Year ending December 31, 2024 | 16,667 |
| Year ending December 31, 2025 | 20,000 |
| Year ending December 31, 2026 | 3,333 |
| Total minimum payments | 40,000 |
| Less unamortized debt discount | (557) |
| Plus accumulated accretion of final fees | 1,206 |
| Less current portion | — |
| Long-term debt, net of current portion | <u>\$ 40,649</u> |

For the years ended December 31, 2022, 2021, and 2020 interest expense related to the Loan Agreement was approximately \$4.1 million, \$3.9 million, and \$1.7 million, respectively.

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Notes to Consolidated Financial Statements (Continued)

9. Property and Equipment

Property and Equipment consist of the following as of December 31, 2022 and 2021 (in thousands):

| | Estimated useful life (in years) | December 31, 2022 | December 31, 2021 |
|-----------------------------------|-------------------------------------|-------------------|-------------------|
| Laboratory equipment | 5 | \$ 9,140 | \$ 7,989 |
| Computer equipment | 3 | 2,036 | 1,979 |
| Furniture and fixtures | 4 | 1,075 | 1,075 |
| Leasehold improvements | * | 11,657 | 11,657 |
| | | 23,908 | 22,700 |
| Less: Accumulated depreciation | | (12,555) | (9,856) |
| Total property and equipment, net | | <u>\$ 11,353</u> | <u>\$ 12,844</u> |

* Leasehold improvements are depreciated over the shorter of the life of the asset and the term of the lease at 7.2 years and 8.2 years as of December 31, 2022 and 2021, respectively. The Company moved into its corporate headquarters in November 2019 and the HQ Lease term ends in February 2030.

Depreciation expense, including depreciation expense for two immaterial capital leases, for the years ended December 31, 2022, 2021 and 2020 was \$2.7 million, \$2.8 million and \$2.8 million, respectively.

10. Accrued Expenses

Accrued expenses consist of the following as of December 31, 2022 and 2021 (in thousands):

| | December 31, 2022 | December 31, 2021 |
|---|-------------------|-------------------|
| External research and preclinical development | \$ 8,219 | \$ 8,274 |
| Employee compensation and benefits | 8,529 | 6,344 |
| Professional fees | 1,164 | 953 |
| Facilities and other | 54 | 53 |
| Accrued expenses | <u>\$ 17,966</u> | <u>\$ 15,624</u> |

11. Commitments and Contingencies

Operating Leases

On January 8, 2019, the Company entered into a lease (the “HQ Lease”) with respect to approximately 52,859 square feet of space in Cambridge, Massachusetts for a lease term commencing in January 2019 and ending in February 2030. The Company has the option to extend the lease term for one additional ten (10) year period. The HQ Lease has escalating rent payments, lease incentives and rent-free periods and the Company records rent expense on a straight-line basis over the term of the HQ Lease, including any rent-free periods.

In connection with the execution of the HQ Lease, the Company was required to provide the landlord with a letter of credit in the amount of \$3.1 million (See Note 7). The Company determined that, for purposes of applying the lease accounting guidance codified in ASU No. 2016-02, Leases (Topic 842) (“ASC 842”), the commencement date of the HQ Lease occurred on May 1, 2019. The Company recorded a right-of-use asset and lease liability of \$15.8 million using an incremental borrowing rate of 9.3%, net of tenant allowances expected to be received of \$9.3 million, on the May 1, 2019 lease commencement date. The Company is amortizing the tenant allowance to offset rent expenses over the term of the HQ Lease starting at the lease commencement date on a straight-line basis. On the Company’s consolidated balance sheets, the Company classified \$2.0 million and \$1.7 million of the lease liability as short-term and \$20.9 million and \$22.9 million of the lease liability as long-term as of December 31, 2022 and 2021, respectively.

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Notes to Consolidated Financial Statements (Continued)

The Company elected the practical expedient provided under ASC 842 and therefore has combined all lease and non-lease components when determining the right-of-use asset and lease liability for the HQ Lease.

Financing Lease

In 2019, the Company entered into equipment lease agreements that have a 48-month term. At the end of the term of these leases, the Company has the right to return the leased equipment, extend the leases, or buy the equipment at the then-current fair market value of the equipment. The Company accounted for these equipment lease agreements as financing leases under ASC 842 and recorded an aggregate financing lease right-of-use assets and corresponding financing lease liabilities of approximately \$1.0 million at the time of executing these leases.

The following is a maturity analysis of the annual undiscounted cash flows reconciled to the carrying value of the operating and financing lease liabilities as of December 31, 2022 (in thousands):

| | Operating | Financing |
|--|------------------|--------------|
| Year ending December 31, 2023 | \$ 4,049 | \$ 66 |
| Year ending December 31, 2024 | 4,166 | — |
| Year ending December 31, 2025 | 4,287 | — |
| Year ending December 31, 2026 | 4,412 | — |
| Year ending December 31, 2027 and beyond | 14,844 | — |
| Total minimum lease payments | 31,758 | 66 |
| Less imputed interest | (8,901) | (1) |
| Total lease liability | <u>\$ 22,857</u> | <u>\$ 65</u> |

The following table outlines the total lease cost for the Company's operating and financing leases as well as weighted average information for these leases as of December 31, 2022 (in thousands):

| | Year Ended December 31, 2022 |
|--|---------------------------------|
| Lease cost: | |
| Operating lease cost | \$ 3,088 |
| Financing lease cost: | |
| Amortization of right-of-use asset | \$ 261 |
| Interest on lease liabilities | 21 |
| Total financing lease cost | <u>\$ 282</u> |
| Cash paid for amounts included in the measurement of liabilities: | |
| Operating cash flows from operating lease | \$ 3,935 |
| Operating cash flows from financing lease | \$ 312 |
| Other information: | Year Ended December 31, 2022 |
| Weighted-average remaining lease term (in years) - operating lease | 7.17 |
| Weighted-average discount rate - operating lease | 9.30 |
| Weighted-average remaining lease term (in years) - financing lease | 0.38 |
| Weighted-average discount rate - financing lease | 9.47 |

Following the adoption of ASC 842, the Company has a right-of-use asset and lease liability that results in recording a temporary tax difference. This temporary tax difference is the result of recognizing a right-of-use asset and related lease liability while such asset and liability have no corresponding tax basis.

Asset Purchase Agreement

Orsenix, LLC

On December 4, 2020, the Company entered into the Asset Purchase Agreement with Orsenix, pursuant to which the Company acquired all of Orsenix's assets related to a novel oral form of arsenic trioxide, which the Company refers to as SY-2101. Under the terms of the Asset Purchase Agreement, the Company is required to pay to Orsenix:

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Notes to Consolidated Financial Statements (Continued)

- an upfront fee of \$12.0 million, which was paid with cash on hand upon the closing of the transaction;
- single-digit million milestone payments related to the development of SY-2101 in indications other than APL;
- \$6.0 million following the achievement of a regulatory milestone related to the development of SY-2101 in APL; and
- up to \$10.0 million upon the achievement of certain commercial milestones with respect to SY-2101.

The Company's obligation to pay the commercial milestone payments expires following the tenth anniversary of the first commercial sale of SY-2101. The Asset Purchase Agreement requires the Company to use commercially reasonable efforts to develop and commercialize SY-2101 for APL in the United States during such period, and to use commercially reasonable efforts to dose the first patient in a Phase 3 clinical trial of SY-2101 on or before the third anniversary of the closing of the transaction; however, the Company retains sole discretion to operate the acquired assets as it determines. The assets acquired from Orsenix do not meet the definition of a business under ASC *Business Combinations* (or ASC 805) because substantially all of the fair value of the assets acquired is concentrated in a single identifiable asset, the rights to SY-2101. Furthermore, as the acquired asset does not include a substantive process, the asset does not meet the minimum requirements to be considered a business under ASC 805. As SY-2101 does not have an alternative future use, the Company recorded the \$12.0 million upfront cash payment as research and development expense on the date of acquisition in December 2020. The Company will expense any future milestone payments made prior to the time an alternative future use for SY-2101 has been established. Once an alternative future use for SY-2101 has been established, the Company will capitalize milestone payments as an addition to the carrying value of SY-2101.

License Agreement

TMRC Co. Ltd.

In September 2015, the Company entered into an exclusive license agreement with TMRC to develop and commercialize tamibarotene in North America and Europe for the treatment of cancer. This agreement was amended and restated in April 2016, and further amended in January 2021 to expand the territory under which the Company is licensed to include Central and South America, Australia, Israel, and Russia.

In exchange for this license, the Company agreed to a non-refundable upfront payment of \$1.0 million, for which \$0.5 million was paid in September 2015 upon execution of the agreement, and the remaining \$0.5 million was paid in May 2016. Under the agreement, the Company is also obligated to make payments upon the successful achievement of clinical and regulatory milestones totaling approximately \$13.0 million per indication, defined as a distinct tumor type. The Company paid \$1.0 million to TMRC for a development milestone achieved upon the successful dosing of the first patient in its Phase 2 clinical trial of tamibarotene in 2016. In May 2021, the Company paid \$2.0 million to TMRC for a development milestone achieved upon the successful dosing of the first patient in its Phase 3 clinical trial of tamibarotene in MDS patients. In September 2021, the Company paid \$1.0 million to TMRC for a development milestone achieved upon the successful dosing of the first patient in its Phase 2 clinical trial of tamibarotene in AML patients. In addition, the Company is obligated to pay TMRC a single-digit percentage royalty, on a country-by-country and product-by-product basis, on net product sales of tamibarotene using know-how and patents licensed from TMRC in North America and Europe for a defined royalty term.

The Company also entered into a supply management agreement with TMRC under which the Company agreed to pay TMRC a fee for each kilogram of tamibarotene that is produced. The Company incurred fees of \$1.8 million, \$0.6 million and \$0.9 million under this supply management agreement during the years ended December 31, 2022, 2021 and 2020, respectively.

Legal Contingencies

From time to time, the Company may be involved in disputes and legal proceedings in the ordinary course of business. The Company does not have any ongoing legal proceedings that, based on its estimates, could have a material effect on its consolidated financial statements. The Company is not party to any litigation and does not have contingency reserves established for any litigation liabilities as of December 31, 2022 or December 31, 2021.

12. Stockholders' equity

Increase of Authorized Shares and Reverse Stock Split

Effective on September 15, 2022, the number of authorized shares of the Company's common stock was increased from 200,000,000 shares (on a pre-split basis) to 700,000,000 shares (on a pre-split basis).

On September 16, 2022, the number of authorized shares of the Company's common stock was proportionately adjusted from 700,000,000 to 70,000,000 as a result of the Reverse Stock Split. Immediately following the Reverse Stock Split, and without giving effect to the shares of the Company's common stock issued in connection with the Merger and the 2022 Private Placement, there were approximately 6.3 million shares of the Company's common stock outstanding. The Company's common stock began trading on The Nasdaq Global Select Market on a split-adjusted basis on September 19, 2022.

No fractional shares were issued in connection with the Reverse Stock Split. Any fractional shares resulting from the Reverse Stock Split were rounded down to the nearest whole number, and each stockholder who would have otherwise been entitled to a fraction of a share of common stock upon the Reverse Stock Split (after aggregating all fractions of a share to which such stockholder would have otherwise been entitled) was, in lieu thereof, entitled to receive a cash payment.

Issuance of Securities through a Private Placement

On September 16, 2022, the Company issued in a private placement 6,387,173 shares of common stock, and, in lieu of shares of common stock, the 2022 Pre-Funded Warrants to purchase an aggregate of 7,426,739 shares of common stock, and, in each case, the accompanying 2022 Warrants to purchase an aggregate of up to 13,813,912 additional shares of common stock (or 2022 Pre-Funded Warrants to purchase common stock in lieu thereof) at a price of \$10.34 per share and accompanying 2022 Warrant (or \$10.33 per 2022 Pre-Funded Warrant and accompanying 2022 Warrant). The 2022 Private Placement resulted in aggregate gross proceeds of \$129.9 million, before \$10.1 million of transaction costs.

On December 8, 2020, through a private placement, the Company issued 1,031,250 shares of common stock, and, in lieu of shares of common stock, 2020 Pre-Funded Warrants to purchase an aggregate of 100,000 shares of common stock, and, in each case, accompanying 2020 Warrants to purchase an aggregate of up to 282,809 additional shares of common stock (or 2020 Pre-Funded Warrants to purchase common stock in lieu thereof) at a price of \$80.00 per share and accompanying 2020 Warrant (or \$79.90 per 2020 Pre-Funded Warrant and accompanying 2020 Warrant). The private placement resulted in aggregate gross proceeds of \$90.5 million, before \$0.4 million of transaction costs.

In the event of certain fundamental transactions involving the Company, the holders of 2022 Warrants and 2020 Warrants may require the Company to make a payment based on a Black-Scholes valuation, using specified inputs. The holders of 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants do not have similar rights. Therefore, the Company accounted for the 2022 Warrants and 2020 Warrants as liabilities, while the 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants met the permanent equity criteria classification. The 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants are classified as a component of permanent equity because they are freestanding financial instruments that are legally detachable and separately exercisable from the shares of common stock with which they were issued, are immediately exercisable, do not embody an obligation for the Company to repurchase its shares, and permit the holders to receive a fixed number of shares of common stock upon exercise. In addition, the 2022 Pre-Funded Warrants and 2020 Pre-Funded Warrants do not provide any guarantee of value or return. The initial fair value of the 2022 Warrants and 2020 Warrants was \$64.7 million and \$19.3 million, respectively, determined using the Black-Scholes valuation model. The Company remeasured the aggregate fair value of the 2022 Warrants and 2020 Warrants at December 31, 2022 and 2021 as \$24.5 million and \$3.0 million, respectively. The change in fair value of \$43.2 million

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(gain), \$16.7 million (gain) and \$0.4 million (loss) was recorded in the Company's statement of operations for the years ended December 31, 2022, 2021, and 2020 respectively.

Issuance of Securities through an Underwritten Public Offering

On January 22, 2021, the Company issued and sold an aggregate of 540,000 shares of its common stock in an underwritten public offering at a public offering price of \$140.00 per share, resulting in gross proceeds of \$75.6 million before deducting underwriting discounts and commissions and other transaction expenses of approximately \$5.1 million.

Convertible Preferred Stock and 2019 Warrants

On April 9, 2019, the Company completed two concurrent underwritten public offerings of its equity securities. In the first public offering, the Company sold 866,733 shares of its common stock and accompanying 2019 Warrants to purchase 195,184 shares of the Company's common stock, at a combined price to the public of \$75.0 per common share and accompanying 2019 Warrant. In the second public offering, the Company sold 666 shares of its Series A Preferred Stock, and accompanying 2019 Warrants to purchase 16,650 shares of the Company's common stock, at a combined public offering price of \$75,000 per share and accompanying 2019 Warrant. The offerings resulted in aggregate gross proceeds to the Company of \$70.0 million, before underwriting discounts and commissions and offering expenses payable by the Company of approximately \$5.0 million.

In November 2019, all 666 shares of Series A Preferred Stock were converted to 66,600 shares of common stock. As of December 31, 2022, there were no shares of Series A Preferred Stock outstanding.

Each 2019 Warrant had an exercise price per share of common stock of \$86.25, subject to adjustment in certain circumstances. Each 2019 Warrant was immediately exercisable upon issuance, provided that the holder was prohibited, subject to certain exceptions, from exercising the 2019 Warrant for shares of the Company's common stock to the extent that immediately prior to or after giving effect to such exercise, the holder, together with its affiliates and other attribution parties, would own more than 4.99% of the total number of shares of the Company's common stock then issued and outstanding. This percentage could be changed at the holders' election to a higher or lower percentage upon 61 days' notice to the Company.

As of December 31, 2022, there are no outstanding 2019 Warrants as the remaining unexercised 2019 Warrants to purchase 211,709 shares of common stock expired on October 10, 2022.

13. Stock-Based Payments

2016 Stock Incentive Plan

The 2016 Stock Incentive Plan (the "2016 Plan") was adopted by the board of directors on December 15, 2015, approved by the stockholders on June 17, 2016, and became effective on July 6, 2016 upon the closing of the Company's initial public offering ("IPO"). The 2016 Plan replaced the 2012 Equity Incentive Plan (the "2012 Plan"). Any options or awards outstanding under the 2012 Plan remained outstanding and effective. The 2016 Plan was replaced by 2022 Equity Incentive Plan on September 16, 2022, and no further awards may be made under the 2016 Plan.

2016 Employee Stock Purchase Plan

The 2016 Employee Stock Purchase Plan (the "2016 ESPP") was adopted by the board of directors on December 15, 2015, approved by the stockholders on June 17, 2016, and became effective on July 6, 2016 upon the closing of the IPO. The number of shares of the Company's common stock reserved for issuance under the 2016 ESPP automatically increases on the first day of each calendar year through the 2025 calendar year, in an amount equal to the least of (i) 117,333 shares of the Company's common stock, (ii) 1.0% of the total number of shares of the Company's common stock outstanding on the first day of the applicable year, and (iii) an amount determined by the Company's board of directors. For the calendar year beginning January 1, 2022, the number of shares reserved for issuance under the 2016 ESPP was increased by 62,024 shares. At December 31, 2022, 237,169 shares remained available for future issuance under the 2016 ESPP.

Inducement Grants

During the year ended December 31, 2021, the Company granted non-statutory stock options to purchase an aggregate of 111,000 shares of the Company's common stock. These stock options were granted outside of the 2016 Plan as an inducement material to the applicable employee's acceptance of employment with the Company in accordance with Nasdaq Listing Rule 5635(c)(4). These stock options will vest over a four-year period, with 25% of the shares underlying each option award vesting on the one-year anniversary of the applicable employee's employment commencement date and the remaining 75% of the shares underlying each award vesting monthly thereafter for three-years. Vesting of each option is subject to such employee's continued service with the Company through the applicable vesting dates.

2022 Inducement Stock Incentive Plan

On January 25, 2022, the Company's board of directors adopted the 2022 Inducement Stock Incentive Plan (the "2022 Plan"), pursuant to which the Company may grant non-statutory stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based awards with respect to an aggregate of 100,000 shares of common stock. Awards under the 2022 Plan may only be granted to persons who (i) were not previously an employee or director of the Company or (ii) are commencing employment with the Company following a bona fide period of non-employment, in either case as an inducement material to the individual's entering into employment with the Company and in accordance with the requirements of Nasdaq Stock Market Rule 5635(c)(4). At December 31, 2022, 22,443 shares remained available for future issuance under the 2022 Plan.

2022 Equity Incentive Plan

The 2022 Stock Incentive Plan (the "2022 EIP") was adopted by the board of directors on July 14, 2022, approved by the stockholders and became effective on September 15, 2022. The 2022 EIP replaced the 2016 Plan. Any options or awards outstanding under the 2016 Plan remained outstanding and effective. Under the 2022 EIP, the Company may grant incentive stock options, non-statutory stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based awards. 4,737,534 shares of the Company's common stock are reserved for issuance under the 2022 EIP. At December 31, 2022, 1,991,628 shares remained available for future issuance under the 2022 EIP. Under the 2022 EIP, stock options may not be granted at less than fair value on the date of grant.

Stock Options

Terms of stock option agreements, including vesting requirements, are determined by the board of directors, subject to the provisions of the applicable plan. Stock option awards granted by the Company generally vest over four years, with 25% vesting on the first anniversary of the vesting commencement date and 75% vesting ratably, on a monthly basis, over the remaining three years. Such awards have a contractual term of ten years from the grant date.

The Company has granted stock options to management for which vesting accelerates upon the achievement of performance-based criteria. Milestone events are specific to the Company's corporate goals, including but not limited to certain clinical development milestones and the Company's ability to execute on its corporate development and financing strategies. Stock-based compensation expense associated with these performance-based stock options is recognized based on the accelerated attribution model. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. Notwithstanding any vesting in accordance with the achievement of performance-based milestones, such awards vest in full on the sixth anniversary of the vesting commencement date. During the year ended December 31, 2020, the Company recorded additional stock-based compensation expense of \$0.4 million related to the acceleration of vesting of certain stock options associated with the initiation of the Phase 3 clinical trial of tamibarotene at the end of 2020 and the entry into the GBT Collaboration Agreement in December 2019, respectively. As of December 31, 2020, there was no unrecognized expense related to the performance-based stock options granted to management. The Company did not grant any performance-based stock option to management during the years ended December 31, 2022 and 2021.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

The Company has granted options to purchase 7,500 shares of common stock to an advisor that vest solely upon the achievement of performance-based criteria. As of December 31, 2022, none of these performance-based criteria had been achieved. As of December 31, 2022, there was \$0.3 million of unrecognized compensation cost related to this option, with a remaining contractual period of 3.7 years.

A summary of the status of stock options as of December 31, 2022 and December 31, 2021 and changes during the year ended December 31, 2022 is presented below:

| | Shares | Weighted Average Exercise Price | Remaining Contractual Life (in years) | Aggregate Intrinsic Value (in thousands) |
|----------------------------------|------------------|---------------------------------------|---|---|
| Outstanding at December 31, 2021 | 665,727 | \$ 82.70 | 7.2 | \$ 4,936 |
| Granted | 1,259,836 | 24.46 | | |
| Exercised | (3,770) | 0.40 | | |
| Cancelled | (194,556) | 83.41 | | |
| Outstanding at December 31, 2022 | <u>1,727,237</u> | \$ 39.94 | 5.7 | \$ — |
| Exercisable at December 31, 2022 | <u>1,057,758</u> | \$ 51.94 | 3.3 | \$ — |

Pursuant to the terms of the Merger Agreement, the Company assumed certain Tyme stock options that were outstanding and unexercised immediately prior to the completion of the Merger. The Company issued options to purchase 692,460 shares of the Company's common stock at the completion of the Merger on September 16, 2022. The original terms and restrictions on such Tyme options shall continue in full force and effect except for certain options held by certain Tyme employees which were modified to extend the exercise period to up to two years. The Company recorded \$0.4 million of one-time additional stock-based compensation expense related to the modification.

The intrinsic value of stock options exercised during the years ended December 31, 2022, 2021 and 2020 was \$0.1 million, \$0.1 million and \$0.8 million, respectively.

As of December 31, 2022, there was \$9.7 million of total unrecognized compensation cost related to non-vested stock options granted to employees, which is expected to be recognized over a weighted-average period of 2.2 years.

Cash received from option exercises during the years ended December 31, 2022, 2021, and 2020 was \$0.1 million, \$0.2 million, and \$1.1 million, respectively.

Restricted Stock Units and Restricted Stock Awards

From time to time, upon approval by the Company's board of directors, certain employees have been granted restricted stock units with time-based vesting criteria. The majority of these restricted stock units vest annually over a four-year term with 25% vesting on each anniversary of the grant date. In addition, pursuant to our director compensation policy, members of our board of directors have been granted, at their election, either restricted stock units or restricted stock awards, which awards vest annually over a three-year term with 33.33% vesting on each anniversary of the grant date. The fair value of restricted stock units and restricted stock awards are calculated based on the closing sale price of the Company's common stock on the date of grant.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

A summary of the status of restricted stock units as of December 31, 2021 and December 31, 2022 and changes during the year ended December 31, 2022 is presented below:

| | Shares Subject to Restricted Stock Units and Restricted Stock Awards | Weighted Average Grant Date Fair Value |
|----------------------------------|---|--|
| Outstanding at December 31, 2021 | 268,749 | \$ 65.21 |
| Granted | 1,109,595 | 8.98 |
| Vested | (86,119) | 72.26 |
| Forfeited | (87,804) | 44.76 |
| Outstanding at December 31, 2022 | <u>1,204,421</u> | <u>\$ 14.68</u> |

As of December 31, 2022, there was \$12.7 million of unrecognized stock-based compensation expense related to outstanding restricted stock units, with an expected recognition period of 2.06 years.

Stock-based Compensation Expense

The fair value of each stock option granted was estimated on the date of grant using the Black-Scholes option-pricing model based on the following weighted-average assumptions:

| | 2022 | Year Ended December 31, 2021 | 2020 |
|--|---------|---------------------------------|---------|
| Weighted-average risk-free interest rate | 3.56 % | 0.99 % | 1.28 % |
| Expected dividend yield | — % | — % | — % |
| Expected option term (in years) | 5.80 | 6.03 | 5.99 |
| Volatility | 83.32 % | 81.56 % | 78.27 % |

The weighted-average grant date fair value per share of options granted in the years ended December 31, 2022, 2021 and 2020 was \$5.99, \$53.30 and \$53.00, respectively.

The following table summarizes the stock-based compensation expense for stock options, restricted stock units and restricted common stock granted to employees and non-employees and from the 2016 ESPP recorded in the Company's statements of operations:

| | 2022 | Year Ended December 31, 2021 | 2020 |
|--|------------------|---------------------------------|------------------|
| Research and development | \$ 5,946 | \$ 5,706 | \$ 4,732 |
| General and administrative | 5,464 | 4,648 | 6,207 |
| Total stock-based compensation expense | <u>\$ 11,410</u> | <u>\$ 10,354</u> | <u>\$ 10,939</u> |

Due to an operating loss, the Company does not record tax benefits associated with stock-based compensation or option exercises. Tax benefits will be recorded when realized.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

14. Income Taxes

The Company accounts for income taxes under FASB Accounting Standards Codification 740 ("ASC 740"). Deferred income tax assets and liabilities are determined based upon differences between financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The components of the income tax provision for the years ended December 31, 2022, 2021 and 2020 are as follows:

| | Year Ended December 31, | | |
|----------|-------------------------|-------------|-------------|
| | 2022 | 2021 | 2020 |
| Current | \$ 3 | \$ 1 | \$ 4 |
| Deferred | — | — | — |
| Total | <u>\$ 3</u> | <u>\$ 1</u> | <u>\$ 4</u> |

A reconciliation of the U.S. statutory income tax rate to the Company's effective tax rate is as follows for the years ended December 31, 2022, 2021 and 2020:

| | 2022 | | Year ended December 31, 2021 | | 2020 |
|---|----------|---|------------------------------------|---|------------|
| Federal income tax computed at federal statutory tax rate | 21.00 | % | 21.00 | % | 21.00 % |
| State income tax, net of federal benefit | 8.09 | | 7.26 | | 6.12 |
| Permanent items | 7.92 | | 3.60 | | (0.68) |
| Federal and state research and development credits | 7.29 | | 5.79 | | 3.89 |
| Rate change | — | | — | | — |
| Expiring Tax Attributed - IRC 382 | (65.82) | | — | | — |
| Stock Option Cancellations | (2.98) | | (0.61) | | (0.29) |
| Other | (0.27) | | (0.80) | | (0.59) |
| Change in valuation allowance | 24.77 | | (36.24) | | (29.45) |
| Effective income tax rate | <u>—</u> | % | <u>—</u> | % | <u>—</u> % |

The principal components of the Company's deferred tax assets and liabilities consist of the following at December 31, 2022 and 2021 (in thousands):

| | 2022 | Year ended December 31, 2021 |
|--|-------------|------------------------------------|
| Deferred tax assets: | | |
| Federal and state net operating loss carryforwards | \$ 81,989 | \$ 109,166 |
| Tax credit carryforwards | 2,263 | 22,446 |
| Capitalized R&D | 27,227 | — |
| Intangible assets | 2,782 | 3,000 |
| Stock-based compensation | 9,035 | 5,700 |
| Deferred revenue | 1,183 | 2,810 |
| Capital lease | 6,262 | 6,812 |
| Other | 2,948 | 2,395 |
| Total deferred tax assets | 133,689 | 152,329 |
| Less valuation allowance | (128,186) | (146,285) |
| Net deferred tax assets | 5,503 | 6,044 |
| Deferred tax liabilities: | | |
| Right-of-use asset | (3,635) | (3,946) |
| Fixed assets | (1,868) | (2,098) |
| Total deferred tax liabilities | (5,503) | (6,044) |
| Net deferred taxes | <u>\$ —</u> | <u>\$ —</u> |

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported if, based on the weight of the evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a valuation allowance against its deferred tax assets at December 31, 2022 and 2021, respectively because the Company's management has determined that it is more likely than not that these assets will not be fully realized. The decrease in the valuation allowance of \$23.5 million in 2022 and \$30.9 million in 2021 primarily relates to the net loss incurred by the Company.

As of December 31, 2022, the Company had federal net operating loss ("NOL") carryforwards of approximately \$300.2 million and state net operating loss carryforwards of \$300.2 million which are available to reduce future taxable income. The Company also had federal tax credits of approximately \$1.9 million and state tax credits of \$0.5 million which may be used to offset future tax liabilities. Federal net operating losses generated before 2018 of approximately \$8.3 million will expire at various dates through 2037, and net operating loss carryforwards of approximately \$292.0 million, which were generated after 2017 have an indefinite carryforward period. Federal tax credits will expire at various dates through 2041. State net operating losses will expire at various dates through 2042. State tax credits will expire at various dates through 2037. The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards are subject to an annual limitation due to certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This limits the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has determined that ownership changes have occurred and as such, the Company's NOLs are limited.

The Company's reserves related to taxes are based on a determination of whether and how much of a tax benefit taken by the Company in its tax filings or positions is more likely than not to be realized following resolution of any potential contingencies present related to the tax benefit. As of December 31, 2022 and 2021, the Company had no unrecognized tax benefits or accrued interest and penalties related to unrecognized tax benefits. The Company's policy is to recognize both interest and penalties related to unrecognized tax benefits in income tax expense.

The Company completed a study to document its qualifying research credits for all years ending before December 31, 2018. For the years ending after December 31, 2017, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an unrecognized tax benefit for the year ended December 31, 2022. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

The federal and state income tax returns are generally subject to examinations for the tax years ended December 31, 2019 through December 31, 2022. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service or state tax authorities to the extent utilized in a future period. The Company files income tax returns in the U.S. federal and various state jurisdictions. There are currently no federal or state audits in process.

15. Defined Contribution Plan

The Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code. This plan covers substantially all employees who meet minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pretax or post-tax basis. Company contributions to the plan may be made at the discretion of the board of directors. The Company instituted effective September 1, 2017 an employer match of 100% of the amount the employees contribute to the 401(k) plan for each payroll period up to the first 1% of plan compensation plus 50% of the amount the employees contribute between 1% and 6% of plan compensation. During the year ended December 31, 2021, the Company revised its employer match to 100% of the amount the employees contribute to the 401(k) plan for each payroll period up to the first 2% of plan compensation plus 50% of the amount the employees contribute between 2% and 6% of plan compensation. For the years ended December 31, 2022, 2021, and 2020 the Company contributed \$1.1 million, \$0.8 million and \$0.5 million respectively, to the 401(k) plan.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Management's Evaluation of Disclosure Controls and Procedures

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our disclosure controls and procedures are designed to provide reasonable assurance of achieving their control objectives.

Our management, with the participation of our Chief Executive Officer, who serves as our principal executive officer, and our Chief Financial Officer, who serves as our principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022, the end of the period covered by this Annual Report. Based upon such evaluation, our chief executive officer and chief financial officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of such date.

Internal Control Over Financial Reporting

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in its 2013 Internal Control — Integrated Framework. Based on our assessment, our management has concluded that, as of December 31, 2022, our internal control over financial reporting is effective based on those criteria.

Changes in Internal Control Over Financial Reporting

During the year ended December 31, 2022, there were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

Not applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item 10 will be included under the captions “Executive Officers,” “Election of Directors” and “Delinquent Section 16(a) Reports,” if applicable, in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics that applies to our officers, including our principal executive, financial and accounting officers, and our directors and employees. We have posted the text of our Code of Business Conduct and Ethics under the “News & Investors— Corporate Governance” section of our website, www.syros.com. We intend to disclose on our website any amendments to, or waivers from, the Code of Business Conduct and Ethics that are required to be disclosed pursuant to the disclosure requirements of Item 5.05 of Form 8-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item 11 will be included under the captions “Executive and Director Compensation” and “Compensation Committee Interlocks and Insider Participation” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and, other than the information required by Item 402(v) of Regulation S-K, is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERSHIP AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this Item 12 will be included under the captions “Security Ownership of Certain Beneficial Owners and Management” and “Securities Authorized for Issuance Under Equity Compensation Plans” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item 13 will be included, as applicable, under the captions “Employment Agreements,” “Potential Payments Upon Termination or Change in Control,” “Board Determination of Independence” and “Related Person Transactions” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this Item 14 will be included under the captions “Audit Fees and Services” and “Pre-Approval Policies and Procedures” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) Financial Statements

For a list of the consolidated financial statements and report of Independent Registered Public Accounting Firm (PCAOB ID:42) included herein, see Index to the Consolidated Financial Statements on page 100 of this Annual Report, which is incorporated into this Item by reference.

(b) Exhibits

| Exhibit No. | Description | Form | Incorporation by Reference | | Filed with this 10-K |
|--|--|-------|----------------------------|----------------|----------------------|
| | | | SEC Filing Date | Exhibit Number | |
| Organizational Documents and Documents Related to Common Stock | | | | | |
| 2.1 | Asset Purchase Agreement, dated December 4, 2020, by and between the Registrant and Orsenix, LLC | 8-K | 12/7/20 | 2.1 | |
| 2.2++ | Agreement and Plan of Merger, dated July 3, 2022, by and among the Registrant, Tack Acquisition Corp. and Tyme Technologies, Inc. | 8-K | 7/5/22 | 2.1 | |
| 3.1 | Restated Certificate of Incorporation of the Registrant, including the Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock of the Registrant | 10-Q | 11/14/22 | 3.1 | |
| 3.2 | Second Amended and Restated Bylaws of the Registrant | 10-Q | 8/5/21 | 3.2 | |
| 4.1 | Description of Securities Registered under Section 12 of the Exchange Act | | | | X |
| 4.2 | Form of Common Stock Certificate | S-1^ | 6/3/16 | 4.1 | |
| 4.3 | Form of Class A Warrant | 8-K | 4/8/19 | 4.1 | |
| 4.4 | Form of Series A Convertible Preferred Stock Certificate | 8-K | 4/8/19 | 4.2 | |
| 4.5 | Form of 2020 Warrant to Purchase Common Stock or 2020 Pre-Funded Warrants | 8-K | 12/7/20 | 4.1 | |
| 4.6 | Form of 2020 Pre-Funded Warrant to Purchase Common Stock | 8-K | 12/7/20 | 4.2 | |
| 4.7 | Sales Agreement dated, June 12, 2020 by and between the Registrant and Cowen and Company, LLC | S-3^^ | 6/12/20 | 1.2 | |
| 4.8 | Securities Purchase Agreement, dated December 4, 2020, by and among the Registrant and the persons party thereto | 8-K | 12/7/20 | 10.1 | |
| 4.9 | Registration Rights Agreement, dated December 4, 2020, by and among the Registrant and the persons party thereto | 8-K | 12/7/20 | 10.2 | |
| 4.10 | Form of 2022 Warrant to Purchase Common Stock or 2022 Pre-Funded Warrants | 8-K | 7/5/22 | 4.1 | |
| 4.11 | Form of 2022 Pre-Funded Warrant to Purchase Common Stock | 8-K | 7/5/22 | 4.2 | |
| 4.12 | Form of Syros Support Agreement | 8-K | 7/5/22 | 10.1 | |
| 4.13 | Form of Tyme Support Agreement | 8-K | 7/5/22 | 10.2 | |
| 4.14 | Form of Lock-up Agreement | 8-K | 7/5/22 | 10.3 | |
| 4.15 | Securities Purchase Agreement, dated July 3, 2022, by and among the Registrant and the persons party thereto | 8-K | 7/5/22 | 10.4 | |
| 4.16 | Registration Rights Agreement, dated July 3, 2022, by and among the Registrant and the persons party thereto | 8-K | 7/5/22 | 10.5 | |
| 4.17 | Registration Rights Agreement, dated July 3, 2022, by and among the Registrant, 667, L.P. and Baker Brothers Life Sciences, L.P. | 8-K | 7/5/22 | 10.5 | |
| Equity Plan Documents | | | | | |
| 10.1* | 2012 Equity Incentive Plan, as amended | S-1^ | 6/3/16 | 10.1 | |
| 10.2* | Form of Incentive Stock Option Agreement under 2012 Equity Incentive Plan | S-1^ | 6/3/16 | 10.2 | |
| 10.3* | Form of Nonstatutory Stock Option Agreement under 2012 Equity Incentive Plan | S-1^ | 6/3/16 | 10.3 | |
| 10.4* | Form of Restricted Stock Agreement under 2012 Equity Incentive Plan | S-1^ | 6/3/16 | 10.4 | |
| 10.5* | 2016 Stock Incentive Plan | S-1^ | 6/3/16 | 10.5 | |

| | | | | | |
|---|---|------|----------|-------|---|
| 10.6* | Form of Incentive Stock Option Agreement under 2016 Stock Incentive Plan | S-1^ | 6/3/16 | 10.6 | |
| 10.7* | Form of Nonstatutory Stock Option Agreement under 2016 Stock Incentive Plan | S-1^ | 6/3/16 | 10.7 | |
| 10.8* | Form of Restricted Stock Unit Agreement under 2016 Stock Incentive Plan | 10-K | 3/7/19 | 10.8 | |
| 10.9* | 2016 Employee Stock Purchase Plan | S-1^ | 6/3/16 | 10.8 | |
| 10.10* | 2022 Inducement Stock Incentive Plan, as amended on January 30, 2023 | | | | X |
| 10.11* | Form of Nonstatutory Stock Option Agreement under 2022 Inducement Stock Incentive Plan | 10-K | 3/15/22 | 10.11 | |
| 10.12* | Form of Restricted Stock Unit Agreement under 2022 Inducement Stock Incentive Plan | 10-K | 3/15/22 | 10.12 | |
| 10.13* | 2022 Equity Incentive Plan | 8-K | 9/15/22 | 99.1 | |
| 10.14* | Form of Stock Option Agreement Under 2022 Equity Incentive Plan | 10-Q | 11/14/22 | 10.10 | |
| 10.15* | Form of Restricted Stock Unit Agreement Under 2022 Equity Incentive Plan | 10-Q | 11/14/22 | 10.11 | |
| 10.16* | Form of Restricted Stock Agreement Under 2022 Equity Incentive Plan | 10-Q | 11/14/22 | 10.12 | |
| 10.17* | Amended and Restated Director Compensation Policy | 10-Q | 11/14/22 | 10.13 | |
| Agreements with Directors and Executive Officers | | | | | |
| 10.18* | Offer Letter, dated November 13, 2012 and effective as of July 2, 2012 by and between the Registrant and Nancy Simonian, M.D., as amended | S-1^ | 6/3/16 | 10.9 | |
| 10.19* | Consulting Agreement dated August 8, 2012 by and between the Registrant and Richard A. Young, Ph.D., as amended | 10-Q | 11/12/19 | 10.1 | |
| 10.20* | Form of Director and Officer Indemnification Agreement by and between the Registrant and each of the directors and executive officers of the Registrant | S-1^ | 6/3/16 | 10.12 | |
| 10.21* | Offer Letter dated April 24, 2013 by and between the Registrant and Eric R. Olson, Ph.D. | 10-K | 3/5/20 | 10.14 | |
| 10.22* | Offer Letter dated December 2, 2015 by and between the Registrant and David A. Roth, M.D., as amended | S-1^ | 6/3/16 | 10.11 | |
| 10.23* | Form of Nonstatutory Stock Option Agreement for Inducement Awards to Executive Officers | 8-K | 10/13/21 | 10.2 | |
| License and Collaboration Agreements | | | | | |
| 10.24+ | Amended and Restated Cancer License Agreement dated April 28, 2016 by and between the Registrant and TMRC Co., Ltd. | 10-K | 3/7/19 | 10.16 | |
| 10.25++ | Amendment No. 1 to Amended and Restated Cancer License Agreement, dated January 8, 2021, by and between the Registrant and TMRC Co., Ltd. | 10-Q | 5/6/21 | 10.1 | |
| 10.26+ | Supply Management Agreement dated April 28, 2016 by and between the Registrant and TMRC Co., Ltd. | S-1^ | 6/3/16 | 10.18 | |
| 10.27 | Consent and Stand-by License Agreement dated April 28, 2016 by and among the Registrant, Toko Pharmaceutical Ind. Co., Ltd. and TMRC Co., Ltd. | S-1^ | 6/3/16 | 10.19 | |
| 10.28+ | Target Discovery, Research Collaboration and Option Agreement dated January 8, 2018 by and between the Registrant and Incyte Corporation | 10-K | 3/12/18 | 10.22 | |
| 10.29++ | Letter Agreement dated November 18, 2019 by and between the Registrant and Incyte Corporation | 10-K | 3/5/20 | 10.21 | |
| 10.30++ | License and Collaboration Agreement dated December 17, 2019 by and between the Registrant and Global Blood Therapeutics, Inc. | 10-K | 3/5/20 | 10.22 | |
| 10.31++ | Master Collaboration Agreement dated March 7, 2022 between the Registrant and Qiagen Manchester Limited | 10-Q | 5/16/22 | 10.1 | |
| Leases and Loan Documents | | | | | |
| 10.32 | Lease dated January 8, 2019 by and between the Registrant and DIV 35 CPD, LLC | 8-K | 1/11/19 | 10.1 | |
| 10.33 | Loan and Security Agreement dated February 12, 2020 by and between the Registrant and Oxford Finance LLC, as collateral agent and lender, as amended | | | | X |
| Subsidiaries, Consents and Certifications | | | | | |
| 21.1 | Subsidiaries of the Registrant | | | | X |
| 23.1 | Consent of Ernst & Young LLP, independent public accounting firm | | | | X |

| | | |
|-------|--|---|
| 31.1 | Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended | X |
| 31.2 | Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended | X |
| 32.1# | Statement of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 | X |
| 32.2# | Statement of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 | X |

XBRL Documents

| | |
|---------|---|
| 101.INS | Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document) |
| 101.SCH | Inline XBRL Taxonomy Extension Schema Document |
| 101.CAL | Inline XBRL Calculation Linkbase Document |
| 101.DEF | Inline XBRL Taxonomy Extension Definition Linkbase Document |
| 101.LAB | Inline XBRL Label Linkbase Document |
| 101.PRE | Inline XBRL Taxonomy Presentation Linkbase Document |
| 104 | Cover Page Interactive Data (formatted as Inline XBRL and contained in Exhibit 101) |

* Indicates management contract or compensatory plan.

+ Confidential treatment has been requested and/or granted as to certain portions, which portions have been omitted and filed separately with the U.S. Securities and Exchange Commission.

++ Portions of this exhibit have been omitted pursuant to Item 601 of Regulation S-K.

^ SEC File No. 333-211818

^^ SEC File No. 333-239141

This certification will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

(c) Financial Statement Schedules

No financial statement schedules have been submitted because they are not required or are not applicable or because the information required is included in the consolidated financial statements or the notes thereto.

ITEM 16. FORM 10-K SUMMARY

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

SYROS PHARMACEUTICALS, INC.

Date: March 2, 2023

By: /s/ Nancy Simonian, M.D.
Nancy Simonian, M.D.
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

| Signature | Title | Date |
|--|--|---------------|
| /s/ Nancy Simonian, M.D. Nancy Simonian, M.D. | President, Chief Executive Officer and Director (<i>Principal Executive Officer</i>) | March 2, 2023 |
| /s/ Jason Haas Jason Haas | Chief Financial Officer (<i>Principal Financial Officer and Principal Accounting Officer</i>) | March 2, 2023 |
| /s/ Peter Wirth Peter Wirth | Chair of the Board of Directors | March 2, 2023 |
| /s/ Srinivas Akkaraju, M.D., Ph.D. Srinivas Akkaraju, M.D., Ph.D. | Director | March 2, 2023 |
| /s/ Mark J. Alles Mark J. Alles | Director | March 2, 2023 |
| /s/ Deborah Dunsire, M.D. Deborah Dunsire, M.D. | Director | March 2, 2023 |
| /s/ S. Gail Eckhardt, M.D. S. Gail Eckhardt, M.D. | Director | March 2, 2023 |
| /s/ Marsha H. Fanucci Marsha H. Fanucci | Director | March 2, 2023 |
| /s/ Andrew Oh Andrew Oh | Director | March 2, 2023 |
| Timothy Tyson | Director | March 2, 2023 |
| /s/ Richard A. Young, Ph.D. Richard A. Young, Ph.D. | Director | March 2, 2023 |

DESCRIPTION OF SECURITIES REGISTERED UNDER SECTION 12 OF THE EXCHANGE ACT

The following description of the common stock, par value \$0.001 per share (the “Common Stock”) of Syros Pharmaceuticals, Inc. (“us,” “our,” “we” or the “Company”), which is the only security of the Company registered under Section 12 of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), summarizes certain information regarding the Common Stock in our Restated Certificate of Incorporation, as amended (the “Certificate of Incorporation”), our Amended and Restated By-laws (the “By-laws”) and applicable provisions of Delaware General Corporation Law (the “DGCL”), and is qualified by reference to the Certificate of Incorporation and the By-laws, which are incorporated by reference as Exhibit 3.1 and Exhibit 3.2, respectively, to the Annual Report on Form 10-K of which this Exhibit 4.1 is a part.

Authorized Capital Stock

Our authorized capital stock consists of 70,000,000 shares of Common Stock and 10,000,000 shares of preferred stock, par value \$0.001 per share (the “Preferred Stock”).

Common Stock

Holders of our Common Stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders is determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Other matters are decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter, except as otherwise disclosed below. Holders of Common Stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding Preferred Stock.

In the event of our liquidation or dissolution, the holders of Common Stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding Preferred Stock. Holders of Common Stock have no preemptive, subscription, redemption or conversion rights, and there are no sinking fund provisions applicable to our Common Stock. The rights, preferences and privileges of holders of Common Stock are subject to and may be adversely affected by the rights of the holders of shares of any series of Preferred Stock that we may designate and issue in the future.

Warrants

Oxford Warrants. On February 12, 2020, the Company entered into a loan and security agreement with Oxford Finance LLC (the “Lender”), pursuant to which a term loan was funded on February 12, 2020 (the “First Tranche”) and another term loan was funded on December 23, 2020 (the “Second Tranche”). In connection with the funding of the First Tranche, the Company issued the Lender warrants to purchase 2,754 shares of Common Stock at an exercise price per share of \$72.60 that will expire on February 12, 2025 (the “First Tranche Warrants”). In connection with the funding of the Second Tranche, the Company Issued the Lender warrants to purchase 1,738 shares of Common Stock at an exercise price of \$115.00 per share that will expire on December 23, 2025 (the “Second Tranche Warrants”, and together with the First Tranche Warrants, the “Oxford Warrants”). As of December 31, 2022, 2,754 First Tranche Warrants and 1,738 Second Tranche Warrants are outstanding and remain unexercised.

2020 Pre-Funded Warrants and 2020 Warrants. On December 8, 2020, through a private placement, the Company issued 1,031,250 shares of Common Stock, and, in lieu of shares of Common Stock, pre-funded warrants (the “2020 Pre-Funded Warrants”) to purchase an aggregate of 100,000 shares of Common Stock, and, in each case, accompanying warrants (the “2020 Warrants”) to purchase an aggregate of up to 282,809 additional shares of Common Stock (or 2020 Pre-Funded Warrants to purchase Common Stock in lieu thereof) at a purchase price of \$80.00 per share and accompanying 2020 Warrant (or \$79.90 per 2020 Pre-Funded Warrant and accompanying 2020 Warrant). The purchase price per 2020 Pre-Funded Warrant and accompanying 2020 Warrant represents the purchase price of \$80.00 per share and accompanying 2020 Warrant minus the \$0.10 per share exercise price of each such 2020 Pre-Funded Warrant. The exercise price of the 2020 Warrants is \$110.00 per share, or if exercised for a 2020 Pre-Funded Warrant in lieu thereof, \$109.90 per 2020 Pre-Funded Warrant (representing the 2020 Warrant exercise price of \$110.00 per share minus the \$0.10 per share exercise price of each such 2020

Pre-Funded Warrant). The 2020 Warrants are exercisable at any time during the period beginning on June 8, 2021 and ending on December 8, 2025. The 2020 Pre-Funded Warrants are exercisable at any time after their original issuance and will not expire. The shares of Common Stock underlying the 2020 Pre-Funded Warrants and the 2020 Warrants have been registered for resale on a Form S-3 resale registration statement which was filed with the SEC and declared effective on January 19, 2021. As of December 31, 2022, 100,000 2020 Pre-Funded Warrants and 282,809 2020 Warrants are outstanding and remain unexercised.

2022 Pre-Funded Warrants and 2022 Warrants. On September 16, 2022, through a private placement, the Company issued 6,387,173 shares of Common Stock, and, in lieu of shares of Common Stock, pre-funded warrants (the “2022 Pre-Funded Warrants”) to purchase an aggregate of 7,426,739 shares of Common Stock, and, in each case, accompanying warrants (the “2022 Warrants”) to purchase an aggregate of up to 13,813,912 additional shares of Common Stock (or 2022 Pre-Funded Warrants to purchase Common Stock in lieu thereof) at a purchase price of \$9.40 per share and accompanying 2022 Warrant (or \$9.399 per 2022 Pre-Funded Warrant and accompanying 2022 Warrant). The purchase price per 2022 Pre-Funded Warrant and accompanying 2022 Warrant represents the purchase price of \$9.40 per share and accompanying 2022 Warrant minus the \$0.001 per share exercise price of each such 2022 Pre-Funded Warrant. The exercise price of the 2022 Warrants is \$10.34 per share, or if exercised for a 2022 Pre-Funded Warrant in lieu thereof, \$10.339 per 2022 Pre-Funded Warrant (representing the 2022 Warrant exercise price of \$10.34 per share minus the \$0.001 per share exercise price of each such 2022 Pre-Funded Warrant). The 2022 Warrants are exercisable at any time during the period beginning on March 16, 2023 and ending on September 16, 2027. The 2022 Pre-Funded Warrants are exercisable at any time after their original issuance and will not expire. The shares of Common Stock underlying the 2022 Pre-Funded Warrants and the 2022 Warrants have been registered for resale on a Form S-3 resale registration statement which was filed with the SEC and declared effective on December 22, 2022. As of December 31, 2022, 7,426,739 2022 Pre-Funded Warrants and 13,813,912 2022 Warrants are outstanding and remain unexercised.

The Company has authorized and reserved for issuance all shares of Common Stock issuable upon exercise of each of the Oxford Warrants, the 2020 Pre-Funded Warrants, the 2020 Warrants, the 2022 Pre-Funded Warrants and the 2022 Warrants (collectively, the “Warrants”). The number of shares of Common Stock to be received upon the exercise of each Warrant may be adjusted from time to time upon the occurrence of certain events, including but not limited to the payment of a dividend or other distribution in respect of Common Stock, subdivisions, reclassifications or combinations of the Common Stock. The securities receivable upon exercise of each Warrant may be adjusted in the event of any reorganization, consolidation, merger, liquidation or similar event.

Anti-Takeover Effects of Delaware Law and Our Charter and By-laws

Delaware law and our Certificate of Incorporation and our By-laws contain provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

Staggered Board; Removal of Directors. Our Certificate of Incorporation and our By-laws divide our board of directors into three classes with staggered three-year terms. In addition, a director may only be removed for cause and only by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in an annual election of directors. Any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may only be filled by vote of a majority of our directors then in office. The classification of our board of directors and the limitations on the removal of directors and filling of vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Stockholder Action by Written Consent; Special Meetings. Our Certificate of Incorporation provides that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of such holders and may not be effected by any consent in writing by such holders. Our Certificate of Incorporation and our By-laws also provide that, except as otherwise required by law, special meetings of our stockholders can only be called by our chairman of the board, our chief executive officer or our board of directors.

Advance Notice Requirements for Stockholder Proposals. Our By-laws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of persons for election to our board of directors. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of

our board of directors or by a stockholder of record on the record date for the meeting who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder's intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities.

Delaware Business Combination Statute. We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless the interested stockholder attained such status with the approval of our board of directors or unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and a sale involving us and the "interested stockholder" of 10% or more of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Amendment of Certificate of Incorporation and By-laws. The DGCL provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's Certificate of Incorporation or By-laws, unless a corporation's Certificate of Incorporation or By-laws, as the case may be, requires a greater percentage. Our By-laws may be amended or repealed by a majority vote of our board of directors or by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our Certificate of Incorporation described above under "—Staggered Board; Removal of Directors" and "—Stockholder Action by Written Consent; Special Meetings."

Authorized but Unissued Shares

The authorized but unissued shares of Common Stock and Preferred Stock are available for future issuance without stockholder approval, subject to any limitations imposed by the listing requirements of The Nasdaq Global Market. These additional shares may be used for a variety of corporate finance transactions, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved Common Stock and Preferred Stock could make it more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

SYROS PHARMACEUTICALS, INC.

2022 INDUCEMENT STOCK INCENTIVE PLAN

1. Purpose

The purpose of this 2022 Inducement Stock Incentive Plan (the “**Plan**”) of Syros Pharmaceuticals, Inc., a Delaware corporation (the “**Company**”), is to advance the interests of the Company’s stockholders by enhancing the Company’s ability to attract, retain and motivate persons who are expected to make important contributions to the Company with an inducement material for such persons to enter into employment with the Company and by providing such persons with equity ownership opportunities and performance-based incentives that are intended to better align the interests of such persons with those of the Company’s stockholders. Except where the context otherwise requires, the term “**Company**” shall include any of the Company’s present or future parent or subsidiary corporations as defined in Sections 424(e) or (f) of the Internal Revenue Code of 1986, as amended, and any regulations thereunder (the “**Code**”) and any other business venture (including, without limitation, joint venture or limited liability company) in which the Company has a controlling interest, as determined by the Board of Directors of the Company (the “**Board**”).

2. Eligibility

Awards under the Plan may only be granted to persons who (a) were not previously an employee or director of the Company or (b) are commencing employment with the Company following a bona fide period of non-employment, in either case as an inducement material to the individual’s entering into employment with the Company and in accordance with the requirements of Nasdaq Stock Market Rule 5635(c)(4). For the avoidance of doubt, neither consultants nor advisors shall be eligible to participate in the Plan. Each person who is granted an Award under the Plan is deemed a “**Participant**.” The Plan provides for the following types of awards, each of which is referred to as an “**Award**”: Options (as defined in Section 5), SARs (as defined in Section 6), Restricted Stock (as defined in Section 7), Restricted Stock Units (as defined in Section 7) and Other Stock-Based Awards (as defined in Section 8).

3. Administration and Delegation

(a) Administration by Board of Directors. The Plan will be administered by the Board. The Board shall have authority to grant Awards and to adopt, amend and repeal such administrative rules, guidelines and practices relating to the Plan as it shall deem advisable. The Board may construe and interpret the terms of the Plan and any Award agreements entered into under the Plan. The Board may correct any defect, supply any omission or reconcile any inconsistency in the Plan or any Award in the manner and to the extent it shall deem expedient and it shall be the sole and final judge of such expediency. All decisions by the Board with respect to the Plan and any Awards shall be made in the Board’s sole discretion and shall be final and binding on all persons having or claiming any interest in the Plan or in any Award.

(b) Appointment of Committees. To the extent permitted by applicable law, the Board may delegate any or all of its powers under the Plan to one or more committees or subcommittees of the Board (a “**Committee**”). All references in the Plan to the “**Board**” shall mean the Board or a Committee of the Board.

4. Stock Available for Awards(a) Number of Shares; Share Counting.

(1) Authorized Number of Shares. Subject to adjustment under Section 9, Awards may be made under the Plan for up to 1,000,000 shares of common stock, \$0.001 par value per share, of the Company (the “**Common Stock**”).

Shares issued under the Plan may consist in whole or in part of authorized but unissued shares or treasury shares.

(2) Share Counting. For purposes of counting the number of shares available for the grant of Awards under the Plan:

(A) all shares of Common Stock covered by SARs shall be counted against the number of shares available for the grant of Awards under the Plan; provided, however, that (i) SARs that may be settled only in cash shall not be so counted and (ii) if the Company grants an SAR in tandem with an Option for the same number of shares of Common Stock and provides that only one such Award may be exercised (a “**Tandem SAR**”), only the shares covered by the Option, and not the shares covered by the Tandem SAR, shall be so counted, and the expiration of one in connection with the other’s exercise will not restore shares to the Plan;

(B) if any Award (i) expires or is terminated, surrendered or canceled without having been fully exercised or is forfeited in whole or in part (including as the result of shares of Common Stock subject to such Award being repurchased by the Company at the original issuance price pursuant to a contractual repurchase right) or (ii) results in any Common Stock not being issued (including as a result of an SAR that was settleable either in cash or in stock actually being settled in cash), the unused Common Stock covered by such Award shall again be available for the grant of Awards; provided, however, that (1) in the case of the exercise of an SAR, the number of shares counted against the shares available under the Plan shall be the full number of shares subject to the SAR multiplied by the percentage of the SAR actually exercised, regardless of the number of shares actually used to settle such SAR upon exercise and (2) the shares covered by a Tandem SAR shall not again become available for grant upon the expiration or termination of such Tandem SAR; and

(C) shares of Common Stock delivered (by actual delivery, attestation, or net exercise) to the Company by a Participant to (i) purchase shares of Common Stock upon the exercise of an Award or (ii) satisfy tax withholding obligations (including shares retained from the Award creating the tax obligation) shall be added back to the number of shares available for the future grant of Awards.

5. Stock Options

(a) General. The Board may grant options to purchase Common Stock (each, an “**Option**”) and determine the number of shares of Common Stock to be covered by each Option, the exercise price of each Option and the conditions and limitations applicable to the exercise of each Option, including conditions relating to applicable federal or state securities laws, as it considers necessary or advisable. All Options under the Plan shall be Nonstatutory Stock Options. A “Nonstatutory Stock Option” is an Option which is not intended to be an “incentive stock option” within the meaning of Section 422 of the Code.

(b) Exercise Price. The Board shall establish the exercise price of each Option and specify the exercise price in the applicable Option agreement. The exercise price shall be not less than 100% of the fair market value per share of Common Stock as determined by (or in a manner approved by) the Board (“**Fair Market Value**”) on the date the Option is granted; provided that if the Board approves the grant of an Option with an exercise price to be determined on a future date, the exercise price shall be not less than 100% of the Fair Market Value on such future date.

(c) Duration of Options. Each Option shall be exercisable at such times and subject to such terms and conditions as the Board may specify in the applicable Option agreement; provided, however, that no Option will be granted with a term in excess of 10 years.

(d) Exercise of Options. Options may be exercised by delivery to the Company of a notice of exercise in a form (which may be electronic) approved by the Company, together with payment in full (in the manner specified in Section 5(e)) of the exercise price for the number of shares for which the Option is exercised. Shares of Common Stock subject to the Option will be delivered by the Company as soon as practicable following exercise.

(e) Payment Upon Exercise. Common Stock purchased upon the exercise of an Option granted under the Plan shall be paid for as follows:

(1) in cash or by check, payable to the order of the Company;

(2) except as may otherwise be provided in the applicable Option agreement or approved by the Board, in its sole discretion, by (i) delivery of an irrevocable and unconditional undertaking by a creditworthy broker to deliver promptly to the Company sufficient funds to pay the exercise price and any required tax withholding or (ii) delivery by the Participant to the Company of a copy of irrevocable and unconditional instructions to a creditworthy broker to deliver promptly to the Company cash or a check sufficient to pay the exercise price and any required tax withholding;

(3) to the extent provided for in the applicable Option agreement or approved by the Board, in its sole discretion, by delivery (either by actual delivery or attestation) of shares of Common Stock owned by the Participant valued at their Fair Market Value, provided (i) such method of payment is then permitted under applicable law, (ii) such Common Stock, if acquired directly from the Company, was owned by the Participant for such minimum period of time, if any, as may be established by the Board in its sole discretion and (iii) such Common Stock is not subject to any repurchase, forfeiture, unfulfilled vesting or other similar requirements;

(4) to the extent provided for in the applicable Option agreement or approved by the Board in its sole discretion, by delivery of a notice of “net exercise” to the Company, as a result of which the Participant would receive (i) the number of shares underlying the portion of the Option being exercised, less (ii) such number of shares as is equal to (A) the aggregate exercise price for the portion of the Option being exercised divided by (B) the Fair Market Value on the date of exercise;

(5) to the extent permitted by applicable law and provided for in the applicable Option agreement or approved by the Board, in its sole discretion, by payment of such other lawful consideration as the Board may determine; or

(6) by any combination of the above permitted forms of payment.

(f) Limitation on Repricing. Unless such action is approved by the Company’s stockholders, the Company may not (except as provided for under Section 9): (1) amend any outstanding Option granted under the Plan to provide an exercise price per share that is lower than the then-current exercise price per share of such outstanding Option, (2) cancel any outstanding option (whether or not granted under the Plan) and grant in substitution therefor new Awards under the Plan covering the same or a different number of shares of Common Stock and having an exercise price per share lower than the then-current exercise price per share of the cancelled option, (3) cancel in exchange for a cash payment any outstanding Option with an exercise price per share above the then-current Fair Market Value or (4) take any other action under the Plan that constitutes a “repricing” within the meaning of the rules of the Nasdaq Stock Market (“*Nasdaq*”).

6. Stock Appreciation Rights

(a) General. The Board may grant Awards consisting of stock appreciation rights (“*SARs*”) entitling the holder, upon exercise, to receive an amount of Common Stock or cash or a combination thereof (such form to be determined by the Board) determined by reference to appreciation, from and after the date of grant, in the Fair Market Value of a share of Common Stock over the measurement price established pursuant to Section 6(b). The date as of which such appreciation is determined shall be the exercise date.

(b) Measurement Price. The Board shall establish the measurement price of each SAR and specify it in the applicable SAR agreement. The measurement price shall not be less than 100% of the Fair Market Value on the date the SAR is granted; provided that if the Board approves the grant of an SAR effective as of a future date, the measurement price shall be not less than 100% of the Fair Market Value on such future date.

(c) Duration of SARs. Each SAR shall be exercisable at such times and subject to such terms and conditions as the Board may specify in the applicable SAR agreement; provided, however, that no SAR will be granted with a term in excess of 10 years.

(d) Exercise of SARs. SARs may be exercised by delivery to the Company of a notice of exercise in a form (which may be electronic) approved by the Company, together with any other documents required by the Board.

(e) Limitation on Repricing. Unless such action is approved by the Company's stockholders, the Company may not (except as provided for under Section 9): (1) amend any outstanding SAR granted under the Plan to provide a measurement price per share that is lower than the then-current measurement price per share of such outstanding SAR, (2) cancel any outstanding SAR (whether or not granted under the Plan) and grant in substitution therefor new Awards under the Plan covering the same or a different number of shares of Common Stock and having an exercise or measurement price per share lower than the then-current measurement price per share of the cancelled SAR, (3) cancel in exchange for a cash payment any outstanding SAR with a measurement price per share above the then-current Fair Market Value or (4) take any other action under the Plan that constitutes a "repricing" within the meaning of the rules of Nasdaq.

7. Restricted Stock; Restricted Stock Units

(a) General. The Board may grant Awards entitling recipients to acquire shares of Common Stock ("**Restricted Stock**"), subject to the right of the Company to repurchase (in accordance with applicable law and the Award agreement) all or part of such shares at their issue price or other stated or formula price (or to require forfeiture of such shares if issued at no cost) from the recipient in the event that conditions specified by the Board in the applicable Award are not satisfied prior to the end of the applicable restriction period or periods established by the Board for such Award. The Board may also grant Awards entitling the recipient to receive shares of Common Stock or cash to be delivered at the time such Award vests ("**Restricted Stock Units**") (Restricted Stock and Restricted Stock Units are each referred to herein as a "**Restricted Stock Award**").

(b) Terms and Conditions for All Restricted Stock Awards. The Board shall determine the terms and conditions of a Restricted Stock Award, including the conditions for vesting and repurchase (or forfeiture) and the issue price, if any.

(c) Additional Provisions Relating to Restricted Stock.

(1) Dividends. Unless otherwise provided in the applicable Award agreement, any dividends (whether paid in cash, stock or property) declared and paid by the Company with respect to shares of Restricted Stock ("**Accrued Dividends**") shall be paid to the Participant only if and when such shares become free from the restrictions on transferability and forfeitability that apply to such shares. Each payment of Accrued Dividends will be made no later than the end of the calendar year in which the dividends are paid to stockholders of that class of stock or, if later, the 15th day of the third month following the lapsing of the restrictions on transferability and the forfeitability provisions applicable to the underlying shares of Restricted Stock.

(2) Stock Certificates. The Company may require that any stock certificates issued in respect of shares of Restricted Stock, as well as dividends or distributions paid on such Restricted Stock, shall be deposited in escrow by the Participant, together with a stock power endorsed in blank, with the Company (or its designee). At the expiration of the applicable restriction periods, the Company (or such designee) shall deliver the certificates no longer subject to such restrictions to the Participant or if the Participant has died, to his or her Designated Beneficiary. "**Designated Beneficiary**" means (i) the beneficiary designated, in a manner determined by the Board, by a Participant to receive amounts due or exercise rights of the Participant in the event of the Participant's death or (ii) in the absence of an effective designation by a Participant, the Participant's estate.

(d) Additional Provisions Relating to Restricted Stock Units.

(1) Settlement. Upon the vesting of and/or lapsing of any other restrictions (i.e., settlement) with respect to each Restricted Stock Unit, the Participant shall be entitled to receive from the Company such number of shares of Common Stock or (if so provided in the applicable Award agreement or otherwise determined by the Board) an amount of cash equal to the Fair Market Value of such number of shares of Common Stock as are set forth in the applicable Restricted Stock Unit agreement, or a combination thereof. The Board may, in its discretion, provide that settlement of Restricted Stock Units shall be deferred, on a mandatory basis or at the election of the Participant in a manner that complies with Section 409A of the Code ("Section 409A").

(2) Voting Rights. A Participant shall have no voting rights with respect to any Restricted Stock Units.

(3) Dividend Equivalents. The Award agreement for Restricted Stock Units may provide Participants with the right to receive an amount equal to any dividends or other distributions declared and paid on an equal number of outstanding shares of Common Stock ("***Dividend Equivalents***"). Dividend Equivalents may be settled in cash and/or shares of Common Stock and shall be subject to the same restrictions on transfer and forfeitability as the Restricted Stock Units with respect to which paid, in each case to the extent provided in the Award agreement.

8. Other Stock-Based Awards

(a) General. Other Awards of shares of Common Stock, and other Awards that are valued in whole or in part by reference to, or are otherwise based on, shares of Common Stock or other property, may be granted hereunder to Participants ("***Other Stock-Based Awards***"). Such Other Stock-Based Awards shall also be available as a form of payment in the settlement of other Awards granted under the Plan or as payment in lieu of compensation to which a Participant is otherwise entitled. Other Stock-Based Awards may be paid in shares of Common Stock or cash, as the Board shall determine.

(b) Terms and Conditions. Subject to the provisions of the Plan, the Board shall determine the terms and conditions of each Other Stock-Based Award, including any purchase price applicable thereto.

9. Adjustments for Changes in Common Stock and Certain Other Events

(a) Changes in Capitalization. In the event of any stock split, reverse stock split, stock dividend, recapitalization, combination of shares, reclassification of shares, spin-off or other similar change in capitalization or event, or any dividend or distribution to holders of Common Stock other than an ordinary cash dividend, (i) the number and class of securities available under the Plan, (ii) the share counting rules set forth in Section 4(a), (iii) the number and class of securities and exercise price per share of each outstanding Option, (iv) the share and per-share provisions and the measurement price of each outstanding SAR, (v) the number of shares subject to and the repurchase price per share subject to each outstanding Restricted Stock Award and (vi) the share and per-share-related provisions and the purchase price, if any, of each outstanding Other Stock-Based Award, shall be equitably adjusted by the Company (or substituted Awards may be made, if applicable) in the manner determined by the Board. Without limiting the generality of the foregoing, in the event the Company effects a split of the Common Stock by means of a stock dividend and the exercise price of and the number of shares subject to an outstanding Option are adjusted as of the date of the distribution of the dividend (rather than as of the record date for such dividend), then an optionee who exercises an Option between the record date and the distribution date for such stock dividend shall be entitled to receive, on the distribution date, the stock dividend with respect to the shares of Common Stock acquired upon such Option exercise, notwithstanding the fact that such shares were not outstanding as of the close of business on the record date for such stock dividend.

(b) Reorganization Events.

(1) Definition. A "***Reorganization Event***" shall mean: (a) any merger or consolidation of the Company with or into another entity as a result of which all of the Common Stock of the Company is converted into or exchanged for the right to receive cash, securities or other property or is cancelled, (b) any transfer or disposition of all of the Common Stock of the Company for cash, securities or other property pursuant to a share exchange or other transaction or (c) any liquidation or dissolution of the Company.

(2) Consequences of a Reorganization Event on Awards Other than Restricted Stock.

(A) In connection with a Reorganization Event, the Board may take any one or more of the following actions as to all or any (or any portion of) outstanding Awards other than Restricted Stock on such terms as the Board determines (except to the extent specifically provided otherwise in an applicable Award agreement or another agreement between the Company and the Participant): (i) provide that such Awards shall be assumed, or substantially equivalent Awards shall be substituted, by the acquiring or succeeding corporation (or an affiliate thereof), (ii) upon written notice to a Participant, provide that all of the Participant's unvested and/or unexercised Awards will terminate immediately prior to the consummation of such Reorganization Event unless exercised by the Participant (to the extent then exercisable) within a specified period following the date of such notice, (iii) provide that outstanding Awards shall become exercisable, realizable, or deliverable, or restrictions applicable to an Award shall lapse, in whole or in part prior to or upon such Reorganization Event, (iv) in the event

of a Reorganization Event under the terms of which holders of Common Stock will receive upon consummation thereof a cash payment for each share surrendered in the Reorganization Event (the “**Acquisition Price**”), make or provide for a cash payment to Participants with respect to each Award held by a Participant equal to (A) the number of shares of Common Stock subject to the vested portion of the Award (after giving effect to any acceleration of vesting that occurs upon or immediately prior to such Reorganization Event) multiplied by (B) the excess, if any, of (I) the Acquisition Price over (II) the exercise, measurement or purchase price of such Award and any applicable tax withholdings, in exchange for the termination of such Award, (v) provide that, in connection with a liquidation or dissolution of the Company, Awards shall convert into the right to receive liquidation proceeds (if applicable, net of the exercise, measurement or purchase price thereof and any applicable tax withholdings) and (vi) any combination of the foregoing. In taking any of the actions permitted under this Section 9(b)(2), the Board shall not be obligated by the Plan to treat all Awards, all Awards held by a Participant, or all Awards of the same type, identically.

(B) Notwithstanding the terms of Section 9(b)(2)(A), in the case of outstanding Restricted Stock Units that are subject to Section 409A of the Code: (i) if the applicable Restricted Stock Unit agreement provides that the Restricted Stock Units shall be settled upon a “change in control event” within the meaning of Treasury Regulation Section 1.409A-3(i)(5)(i), and the Reorganization Event constitutes such a “change in control event”, then no assumption or substitution shall be permitted pursuant to Section 9(b)(2)(A)(i) and the Restricted Stock Units shall instead be settled in accordance with the terms of the applicable Restricted Stock Unit agreement; and (ii) the Board may only undertake the actions set forth in clauses (iii), (iv) or (v) of Section 9(b)(2)(A) if the Reorganization Event constitutes a “change in control event” as defined under Treasury Regulation Section 1.409A-3(i)(5)(i) and such action is permitted or required by Section 409A of the Code; if the Reorganization Event is not a “change in control event” as so defined or such action is not permitted or required by Section 409A of the Code, and the acquiring or succeeding corporation does not assume or substitute the Restricted Stock Units pursuant to clause (i) of Section 9(b)(2)(A), then the unvested Restricted Stock Units shall terminate immediately prior to the consummation of the Reorganization Event without any payment in exchange therefor.

(C) For purposes of Section 9(b)(2)(A)(i), an Award (other than Restricted Stock) shall be considered assumed if, following consummation of the Reorganization Event, such Award confers the right to purchase or receive pursuant to the terms of such Award, for each share of Common Stock subject to the Award immediately prior to the consummation of the Reorganization Event, the consideration (whether cash, securities or other property) received as a result of the Reorganization Event by holders of Common Stock for each share of Common Stock held immediately prior to the consummation of the Reorganization Event (and if holders were offered a choice of consideration, the type of consideration chosen by the holders of a majority of the outstanding shares of Common Stock); provided, however, that if the consideration received as a result of the Reorganization Event is not solely common stock of the acquiring or succeeding corporation (or an affiliate thereof), the Company may, with the consent of the acquiring or succeeding corporation, provide for the consideration to be received upon the exercise or settlement of the Award to consist solely of such number of shares of common stock of the acquiring or succeeding corporation (or an affiliate thereof) that the Board determines to be equivalent in value (as of the date of such determination or another date specified by the Board) to the per share consideration received by holders of outstanding shares of Common Stock as a result of the Reorganization Event.

(3) Consequences of a Reorganization Event on Restricted Stock. Upon the occurrence of a Reorganization Event other than a liquidation or dissolution of the Company, the repurchase and other rights of the Company with respect to outstanding Restricted Stock shall inure to the benefit of the Company’s successor and shall, unless the Board determines otherwise, apply to the cash, securities or other property which the Common Stock was converted into or exchanged for pursuant to such Reorganization Event in the same manner and to the same extent as they applied to such Restricted Stock; provided, however, that the Board may provide for termination or deemed satisfaction of such repurchase or other rights under the instrument evidencing any Restricted Stock or any other agreement between a Participant and the Company, either initially or by amendment. Upon the occurrence of a Reorganization Event involving the liquidation or dissolution of the Company, except to the extent specifically provided to the contrary in the instrument evidencing any Restricted Stock or any other agreement between a Participant and the Company, all restrictions and conditions on all Restricted Stock then outstanding shall automatically be deemed terminated or satisfied.

10. General Provisions Applicable to Awards

(a) Transferability of Awards. Awards shall not be sold, assigned, transferred, pledged or otherwise encumbered by the person to whom they are granted, either voluntarily or by operation of law, except by will or the

laws of descent and distribution or, pursuant to a qualified domestic relations order, and, during the life of the Participant, shall be exercisable only by the Participant; provided, however, that the Board may permit or provide in an Award for the gratuitous transfer of the Award by the Participant to or for the benefit of any immediate family member, family trust or other entity established for the benefit of the Participant and/or an immediate family member thereof if the Company would be eligible to use a Form S-8 under the Securities Act of 1933, as amended, for the registration of the sale of the Common Stock subject to such Award to such proposed transferee; provided further, that the Company shall not be required to recognize any such permitted transfer until such time as such permitted transferee shall, as a condition to such transfer, deliver to the Company a written instrument in form and substance satisfactory to the Company confirming that such transferee shall be bound by all of the terms and conditions of the Award. References to a Participant, to the extent relevant in the context, shall include references to authorized transferees. For the avoidance of doubt, nothing contained in this Section 10(a) shall be deemed to restrict a transfer to the Company.

(b) Documentation; Press Release. Each Award shall be evidenced in such form (written, electronic or otherwise) as the Board shall determine. Each Award may contain terms and conditions in addition to those set forth in the Plan. Promptly following the grant of an Award hereunder, the Company must disclose in a press release the material terms of the grant, the number of shares involved, and, if required by law or the rules of Nasdaq, the identity of the Participant and each Participant, by accepting the Award, consents to the foregoing.

(c) Board Discretion. Except as otherwise provided by the Plan, each Award may be made alone or in addition or in relation to any other Award. The terms of each Award need not be identical, and the Board need not treat Participants uniformly.

(d) Termination or Change of Status. The Board shall determine, either at the time an Award is granted or thereafter, the effect on an Award of the disability, death, termination or other cessation of employment, authorized leave of absence or other change in the employment or other status of a Participant and the extent to which, and the period during which, the Participant, or the Participant's legal representative, conservator, guardian or Designated Beneficiary, may exercise rights under the Award.

(e) Withholding. The Participant must satisfy all applicable federal, state, and local or other income and employment tax withholding obligations before the Company will deliver stock certificates or otherwise recognize ownership of Common Stock under an Award. The Company may decide to satisfy the withholding obligations through additional withholding on salary or wages. If the Company elects not to or cannot withhold from other compensation, the Participant must pay the Company the full amount, if any, required for withholding or have a broker tender to the Company cash equal to the withholding obligations. Payment of withholding obligations is due before the Company will issue any shares on exercise, vesting or release from forfeiture of an Award or at the same time as payment of the exercise or purchase price, unless the Company determines otherwise. If provided for in an Award or approved by the Board in its sole discretion, a Participant may satisfy such tax obligations in whole or in part by delivery (either by actual delivery or attestation) of shares of Common Stock, including shares retained from the Award creating the tax obligation, valued at their Fair Market Value; provided, however, except as otherwise provided by the Board, that the total tax withholding where stock is being used to satisfy such tax obligations cannot exceed the Company's minimum statutory withholding obligations (based on minimum statutory withholding rates for federal and state tax purposes, including payroll taxes, that are applicable to such supplemental taxable income). Shares used to satisfy tax withholding requirements cannot be subject to any repurchase, forfeiture, unfulfilled vesting or other similar requirements.

(f) Amendment of Award. Except as otherwise provided in Sections 5(f) and 6(e) with respect to repricings, the Board may amend, modify or terminate any outstanding Award, including but not limited to, substituting therefor another Award of the same or a different type and changing the date of exercise or realization, provided that no amendment that would require stockholder approval under the rules of Nasdaq may be made effective unless and until the Company's stockholders approve such amendment. The Participant's consent to such action shall be required unless (i) the Board determines that the action, taking into account any related action, does not materially and adversely affect the Participant's rights under the Plan or (ii) the change is permitted under Section 9.

(g) Conditions on Delivery of Stock. The Company will not be obligated to deliver any shares of Common Stock pursuant to the Plan or to remove restrictions from shares previously issued or delivered under the Plan until (i) all conditions of the Award have been met or removed to the satisfaction of the Company, (ii) in the

opinion of the Company's counsel, all other legal matters in connection with the issuance and delivery of such shares have been satisfied, including any applicable securities laws and regulations and any applicable stock exchange or stock market rules and regulations and (iii) the Participant has executed and delivered to the Company such representations or agreements as the Company may consider appropriate to satisfy the requirements of any applicable laws, rules or regulations.

(h) Acceleration. The Board may at any time provide that any Award shall become immediately exercisable in whole or in part, free of some or all restrictions or conditions, or otherwise realizable in whole or in part, as the case may be.

11. Miscellaneous

(a) No Right To Employment or Other Status. No person shall have any claim or right to be granted an Award by virtue of the adoption of the Plan, and the grant of an Award shall not be construed as giving a Participant the right to continued employment or any other relationship with the Company. The Company expressly reserves the right at any time to dismiss or otherwise terminate its relationship with a Participant free from any liability or claim under the Plan, except as expressly provided in the applicable Award.

(b) No Rights As Stockholder; Clawback Policy. Subject to the provisions of the applicable Award, no Participant or Designated Beneficiary shall have any rights as a stockholder with respect to any shares of Common Stock to be distributed with respect to an Award until becoming the record holder of such shares. In accepting an award under the Plan, a Participant shall agree to be bound by any clawback policy the Company may adopt in future.

(c) Effective Date and Term of Plan. The Plan shall become effective on the date on which it is adopted by the Board (the "**Effective Date**"). It is expressly intended that approval of the Company's stockholders not be required as a condition to the effectiveness of the Plan, and the Plan's provisions shall be interpreted in a manner consistent with such intent for all purposes.

(d) Amendment of Plan. The Board may amend, suspend or terminate the Plan or any portion thereof at any time provided that no amendment that would require stockholder approval under the rules of Nasdaq may be made effective unless and until the Company's stockholders approve such amendment. Unless otherwise specified in the amendment, any amendment to the Plan adopted in accordance with this Section 11(d) shall apply to, and be binding on the holders of, all Awards outstanding under the Plan at the time the amendment is adopted, provided the Board determines that such amendment, taking into account any related action, does not materially and adversely affect the rights of Participants under the Plan.

(e) Authorization of Sub-Plans (including for Grants to non-U.S. Employees). The Board may from time to time establish one or more sub-plans under the Plan for purposes of satisfying applicable securities, tax or other laws of various jurisdictions. The Board shall establish such sub-plans by adopting supplements to the Plan containing (i) such limitations on the Board's discretion under the Plan as the Board deems necessary or desirable or (ii) such additional terms and conditions not otherwise inconsistent with the Plan as the Board shall deem necessary or desirable. All supplements adopted by the Board shall be deemed to be part of the Plan, but each supplement shall apply only to Participants within the affected jurisdiction and the Company shall not be required to provide copies of any supplement to Participants in any jurisdiction which is not the subject of such supplement.

(f) Compliance with Section 409A of the Code. Except as provided in individual Award agreements initially or by amendment, if and to the extent (i) any portion of any payment, compensation or other benefit provided to a Participant pursuant to the Plan in connection with his or her employment termination constitutes "nonqualified deferred compensation" within the meaning of Section 409A of the Code and (ii) the Participant is a specified employee as defined in Section 409A(a)(2)(B)(i) of the Code, in each case as determined by the Company in accordance with its procedures, by which determinations the Participant (through accepting the Award) agrees that he or she is bound, such portion of the payment, compensation or other benefit shall not be paid before the day that is six months plus one day after the date of "separation from service" (as determined under Section 409A of the Code) (the "**New Payment Date**"), except as Section 409A of the Code may then permit. The aggregate of any payments that otherwise would have been paid to the Participant during the period between the date of separation from service and the New Payment Date shall be paid to the Participant in a lump sum on such New Payment Date, and any remaining payments will be paid on their original schedule.

The Company makes no representations or warranty and shall have no liability to the Participant or any other person if any provisions of or payments, compensation or other benefits under the Plan are determined to constitute nonqualified deferred compensation subject to Section 409A of the Code but do not to satisfy the conditions of that section.

(g) Effect on Other Employee Benefit Plans. The value of any Award issued to a Participant and the Shares issuable or amounts payable thereunder shall not be included as compensation, earnings, salaries or other similar terms used when calculating benefits under any employee benefit plan (other than the Plan) sponsored by the Company, except as such plans otherwise expressly provide.

(h) Limitations on Liability. Notwithstanding any other provisions of the Plan, no individual acting as a director, officer, employee or agent of the Company will be liable to any Participant, former Participant, spouse, beneficiary, or any other person for any claim, loss, liability, or expense incurred in connection with the Plan, nor will such individual be personally liable with respect to the Plan because of any contract or other instrument he or she executes in his or her capacity as a director, officer, employee or agent of the Company. The Company will indemnify and hold harmless each director, officer, employee or agent of the Company to whom any duty or power relating to the administration or interpretation of the Plan has been or will be delegated, against any cost or expense (including attorneys' fees) or liability (including any sum paid in settlement of a claim with the Board's approval) arising out of any act or omission to act concerning the Plan unless arising out of such person's own fraud or bad faith.

(i) Governing Law. The provisions of the Plan and all Awards made hereunder shall be governed by and interpreted in accordance with the laws of the State of Delaware, excluding choice-of-law principles of the law of such state that would require the application of the laws of a jurisdiction other than the State of Delaware.

Syros Pharmaceuticals, Inc.
Amendment No. 1 to 2022 Inducement Stock Incentive Plan

Syros Pharmaceuticals, Inc.'s (the "Company") 2022 Inducement Stock Incentive Plan (the "Inducement Plan"), pursuant to Section 11(d) thereof, is hereby amended as follows:

1. Section 4(a) of the Inducement Plan be, and hereby is, amended by increasing the maximum number of shares of common stock, \$0.001 par value per share, of the Company (the "Common Stock") reserved under the Inducement Plan for Awards (as defined in the Inducement Plan) from 100,000 shares of Common Stock to 850,000 shares of Common Stock.

Adopted by the Compensation Committee of the Board of Directors: January 30, 2023

LOAN AND SECURITY AGREEMENT

THIS LOAN AND SECURITY AGREEMENT (as the same may from time to time be amended, modified, supplemented or restated, this “**Agreement**”) dated as of February 12, 2020 (the “**Effective Date**”) among OXFORD FINANCE LLC, a Delaware limited liability company with an office located at 133 North Fairfax Street, Alexandria, Virginia 22314 (“**Oxford**”), as collateral agent (in such capacity, “**Collateral Agent**”), the Lenders listed on Schedule 1.1 hereof or otherwise a party hereto from time to time including Oxford in its capacity as a Lender (each a “**Lender**” and collectively, the “**Lenders**”), and SYROS PHARMACEUTICALS, INC., a Delaware corporation with offices located at 35 CambridgePark Drive, 4th Floor, Cambridge, MA 02140 (“**Borrower**”), provides the terms on which the Lenders shall lend to Borrower and Borrower shall repay the Lenders. The parties agree as follows:

1. ACCOUNTING AND OTHER TERMS

1.1 Accounting terms not defined in this Agreement shall be construed in accordance with GAAP. Calculations and determinations must be made in accordance with GAAP. Capitalized terms not otherwise defined in this Agreement shall have the meanings set forth in Section 13. All other terms contained in this Agreement, unless otherwise indicated, shall have the meaning provided by the Code to the extent such terms are defined therein. All references to “**Dollars**” or “**\$**” are United States Dollars, unless otherwise noted.

2. LOANS AND TERMS OF PAYMENT

2.1 Promise to Pay. Borrower hereby unconditionally promises to pay each Lender, the outstanding principal amount of all Term Loans advanced to Borrower by such Lender and accrued and unpaid interest thereon and any other amounts due hereunder as and when due in accordance with this Agreement.

2.2 Term Loans.

(a) Availability.

(i) Subject to the terms and conditions of this Agreement, the Lenders agree, severally and not jointly, on the Effective Date, to make one (1) term loan to Borrower in an aggregate amount of Twenty Million Dollars (\$20,000,000.00) according to each Lender’s Term A Loan Commitment as set forth on Schedule 1.1 hereto (the “**Term A Loan**”). After repayment, the Term A Loan may not be re-borrowed.

(ii) Subject to the terms and conditions of this Agreement, the Lenders agree, severally and not jointly, during the Term B Draw Period, to make one (1) term loan to Borrower in an aggregate amount of Twenty Million Dollars (\$20,000,000.00) according to each Lender’s Term B Loan Commitment as set forth on Schedule 1.1 hereto (the “**Term B Loan**”). After repayment, the Term B Loan may not be re-borrowed.

(iii) Subject to the terms and conditions of this Agreement, the Lenders may, in their sole discretion, agree to make one (1) term loan to Borrower in an aggregate amount of Twenty Million Dollars (\$20,000,000.00), and, when made, according to a commitment schedule to be provided by the Lenders prior to the Funding Date of such term loans (the “**Term C Loan**”; each Term A Loan, Term B Loan and Term C Loan is hereinafter referred to singly as a “**Term Loan**” and the Term A Loan, the Term B Loan and the Term C Loan are hereinafter referred to collectively as the “**Term Loans**”). After repayment, no Term C Loan may be re-borrowed.

(b) Repayment. Borrower shall make monthly payments of interest only commencing on the first (1st) Payment Date following the Funding Date of each Term Loan, and continuing on the Payment Date of each successive month thereafter through and including the Payment Date immediately preceding the Amortization Date. Borrower agrees to pay, on the Funding Date of each Term Loan, any initial partial monthly interest payment otherwise due for the period between the Funding Date of such Term Loan and the first Payment Date thereof. Commencing on the Amortization Date, and continuing on the Payment Date of each month thereafter, Borrower shall make consecutive equal monthly payments of principal, together with applicable interest, in arrears, to each Lender, as calculated by Collateral Agent (which calculations shall be deemed correct absent manifest error) based upon: (1) the amount of such Lender’s Term Loan, (2) the effective rate of interest, as determined in Section 2.3(a),

and (3) a repayment schedule equal to twenty-four (24) months. All unpaid principal and accrued and unpaid interest with respect to each Term Loan is due and payable in full on the Maturity Date. Each Term Loan may only be prepaid in accordance with Sections 2.2(c) and 2.2(d).

(c) Mandatory Prepayments. If the Term Loans are accelerated following the occurrence of an Event of Default, Borrower shall immediately pay to Lenders, payable to each Lender in accordance with its respective Pro Rata Share, an amount equal to the sum of: (i) all outstanding principal of the Term Loans plus accrued and unpaid interest thereon through the prepayment date, (ii) the Final Payment, (iii) the Prepayment Fee, plus (iv) all other Obligations that are due and payable, including Lenders' Expenses and interest at the Default Rate with respect to any past due amounts. Notwithstanding (but without duplication with) the foregoing, on the Maturity Date, if the Final Payment had not previously been paid in full in connection with the prepayment of the Term Loans in full, Borrower shall pay to Collateral Agent, for payment to each Lender in accordance with its respective Pro Rata Share, the Final Payment in respect of the Term Loan(s).

(d) Permitted Prepayment of Term Loans.

(i) Borrower shall have the option to prepay all, but not less than all, of the Term Loans advanced by the Lenders under this Agreement, provided Borrower (i) provides written notice to Collateral Agent of its election to prepay the Term Loans at least ten (10) days prior to such prepayment, and (ii) pays to the Lenders on the date of such prepayment, payable to each Lender in accordance with its respective Pro Rata Share, an amount equal to the sum of (A) all outstanding principal of the Term Loans plus accrued and unpaid interest thereon through the prepayment date, (B) the Final Payment, (C) the Prepayment Fee, plus (D) all other Obligations that are due and payable, including Lenders' Expenses and interest at the Default Rate with respect to any past due amounts.

(ii) Notwithstanding anything herein to the contrary, Borrower shall also have the option to prepay part of the Term Loans advanced by the Lenders under this Agreement, provided Borrower (i) shall make no more than two (2) prepayments during the life of this Agreement, (ii) provides written notice of its election to prepay the Term Loans at least ten (10) days prior to such prepayment, (iii) prepays such part of the Term Loans in a denomination that is not less than Five Million Dollars (\$5,000,000.00) or, if in excess thereof, in integral whole number multiples of One Million Dollars (\$1,000,000.00) in excess thereof, and (iv) pays to the Lenders on the date of such prepayment, payable to each Lender in accordance with its respective Pro Rata Share, an amount equal to the sum of (A) the portion of outstanding principal of such Term Loans plus all accrued and unpaid interest thereon through the prepayment date, (B) the applicable Final Payment, and (C) all other Obligations that are then due and payable, including Lenders' Expenses and interest at the Default Rate with respect to any past due amounts, (D) the applicable Prepayment Fee with respect to the portion of such Term Loans being prepaid, and (E) a portion of any fee that would have otherwise been due pursuant to Section 2.2(d)(i). For the purposes of clarity, any partial prepayment shall be applied pro-rata to all outstanding amounts under each Term Loan, and shall be applied pro-rata within each Term Loan tranche to reduce amortization payments under Section 2.2(b) on a pro-rata basis.

2.3 Payment of Interest on the Credit Extensions.

(a) Interest Rate. Subject to Section 2.3(b), the principal amount outstanding under the Term Loans shall accrue interest at a floating per annum rate equal to the Basic Rate, determined by Collateral Agent on the Funding Date of the applicable Term Loan, which interest shall be payable monthly in arrears in accordance with Sections 2.2(b) and 2.3(e). Interest shall accrue on each Term Loan commencing on, and including, the Funding Date of such Term Loan, and shall accrue on the principal amount outstanding under such Term Loan through and including the day on which such Term Loan is paid in full.

(b) Default Rate. Immediately upon the occurrence and during the continuance of an Event of Default, Obligations shall accrue interest at a floating per annum rate equal to the rate that is otherwise applicable thereto plus five percentage points (5.00%) (the "**Default Rate**"). Payment or acceptance of the increased interest rate provided in this Section 2.3(b) is not a permitted alternative to timely payment and shall not constitute a waiver of any Event of Default or otherwise prejudice or limit any rights or remedies of Collateral Agent.

(c) 360-Day Year. Interest shall be computed on the basis of a three hundred sixty (360) day year, and the actual number of days elapsed.

(d) Debit of Accounts. Collateral Agent and each Lender may debit (or ACH) any deposit accounts, maintained by Borrower or any of its Subsidiaries, including the Designated Deposit Account, for principal and interest payments or any other amounts Borrower owes the Lenders under the Loan Documents when due. Any such debits (or ACH activity) shall not constitute a set-off.

(e) Payments. Except as otherwise expressly provided herein, all payments by Borrower under the Loan Documents shall be made to the respective Lender to which such payments are owed, at such Lender's office in immediately available funds on the date specified herein. Unless otherwise provided, interest is payable monthly on the Payment Date of each month. Payments of principal and/or interest received after 2:00 p.m. Eastern time are considered received at the opening of business on the next Business Day. When a payment is due on a day that is not a Business Day, the payment is due the next Business Day and additional fees or interest, as applicable, shall continue to accrue until paid. All payments to be made by Borrower hereunder or under any other Loan Document, including payments of principal and interest, and all fees, expenses, indemnities and reimbursements, shall be made without set-off, recoupment or counterclaim, in lawful money of the United States and in immediately available funds.

2.4 Secured Promissory Notes. The Term Loans shall be evidenced by a Secured Promissory Note or Notes in the form attached as Exhibit D hereto (each a "**Secured Promissory Note**"), and shall be repayable as set forth in this Agreement. Borrower irrevocably authorizes each Lender to make or cause to be made, on or about the Funding Date of any Term Loan or at the time of receipt of any payment of principal on such Lender's Secured Promissory Note, an appropriate notation on such Lender's Secured Promissory Note Record reflecting the making of such Term Loan or (as the case may be) the receipt of such payment. The outstanding amount of each Term Loan set forth on such Lender's Secured Promissory Note Record shall be prima facie evidence of the principal amount thereof owing and unpaid to such Lender, but the failure to record, or any error in so recording, any such amount on such Lender's Secured Promissory Note Record shall not limit or otherwise affect the obligations of Borrower under any Secured Promissory Note or any other Loan Document to make payments of principal or interest on any Secured Promissory Note when due. Upon receipt of an affidavit of an officer of a Lender as to the loss, theft, destruction, or mutilation of its Secured Promissory Note, Borrower shall issue, in lieu thereof, a replacement Secured Promissory Note in the same principal amount thereof and of like tenor.

2.5 Fees. Borrower shall pay to Collateral Agent:

(a) Facility Fee. A fully earned, non-refundable facility fee (the "**Facility Fee**") to be shared between the Lenders pursuant to their respective Commitment Percentages payable as follows: (i) One Hundred Thousand Dollars (\$100,000.00) of the Facility Fee shall be due and payable on the Effective Date, (ii) Seventy-Five Thousand Dollars (\$75,000.00) of the Facility Fee shall be due and payable on the Funding Date of the Term B Loans, and (iii) Fifty Thousand Dollars (\$50,000.00) of the Facility Fee shall be due and payable on the Funding Date of the Term C Loans;

(b) Final Payment. The Final Payment, when due hereunder, to be shared between the Lenders in accordance with their respective Pro Rata Shares;

(c) Prepayment Fee. The Prepayment Fee, when due hereunder, to be shared between the Lenders in accordance with their respective Pro Rata Shares;

(d) Good Faith Deposit. Borrower has paid to Collateral Agent a deposit of Fifty Thousand Dollars (\$50,000.00) (the "**Good Faith Deposit**"), to initiate the Collateral Agent's and Lenders' due diligence review and documentation process. The Good Faith Deposit shall be utilized to pay Lenders' Expenses; and

(e) Lenders' Expenses. All Lenders' Expenses (including reasonable and documented attorneys' fees and expenses for documentation and negotiation of this Agreement) incurred through and after the Effective Date, when due.

2.6 Withholding. Payments received by the Lenders from Borrower hereunder will be made free and clear of and without deduction for any and all present or future taxes, levies, imposts, duties, deductions, withholdings, assessments, fees or other charges imposed by any governmental authority (including any interest, additions to tax or penalties applicable thereto, collectively, "**Taxes**"). Specifically, however, if at any time any Governmental

Authority, applicable law, regulation or international agreement requires Borrower to make any withholding or deduction from any such payment or other sum payable hereunder to the Lenders, Borrower hereby covenants and agrees that the amount due from Borrower with respect to such payment or other sum payable hereunder will be increased to the extent necessary to ensure that, after the making of such required withholding or deduction, each Lender receives a net sum equal to the sum which it would have received had no withholding or deduction been required and Borrower shall pay the full amount withheld or deducted to the relevant Governmental Authority; provided, however, Borrower shall not be required to pay any additional amount to any Lender with respect to Excluded Taxes. Borrower will, upon request, furnish the Lenders with proof reasonably satisfactory to the Lenders indicating that Borrower has made such withholding payment; provided, however, that Borrower need not make any withholding payment if the amount or validity of such withholding payment is contested in good faith by appropriate and timely proceedings and as to which payment in full is bonded or reserved against by Borrower. The agreements and obligations of Borrower contained in this Section 2.6 shall survive the termination of this Agreement.

On the date of this Agreement, each Lender shall deliver to Borrower a complete and properly executed IRS Form W-9. If any assignee of a Lender's rights under Section 12.1 of this Agreement is not a "United States Person" as defined in Section 7701(a)(30) of the U.S. Internal Revenue Code ("Non-U.S. Lender"), such Non-U.S. Lender shall, upon becoming party to this Agreement, deliver to Borrower a complete and properly executed IRS Form W-8BEN-E (or W-8BEN, as applicable), W-8ECI or W-8IMY, as appropriate, or any successor form prescribed by the IRS, certifying that such Non-U.S. Lender is entitled to an exemption from U.S. withholding tax on interest and other amounts payable under this Agreement. Notwithstanding the foregoing, (i) Borrower shall not be required to pay any additional amount to any Non-U.S. Lender hereunder if such Non-U.S. Lender fails or is unable to deliver the forms, certificates or other evidence described in the preceding sentence, unless such Non-U.S. Lender's failure or inability to deliver such forms is the result of any change in any applicable law, treaty or governmental rule, or any change in the interpretation thereof after such Non-U.S. Lender became a party to this Agreement and (ii) Borrower shall not be required to pay any additional amount to any Non-U.S. Lender hereunder with respect to taxes imposed under Sections 1471 through 1474 of the U.S. Internal Revenue Code, as of the date of this Agreement (or any amended or successor version that is substantively comparable and not materially more onerous to comply with) and any current or future regulations or official interpretations thereof.

3. CONDITIONS OF LOANS

3.1 Conditions Precedent to Initial Credit Extension. Each Lender's obligation to make the Term A Loan is subject to the condition precedent that Collateral Agent and each Lender shall consent to or shall have received, in form and substance reasonably satisfactory to Collateral Agent and each Lender, such documents, and completion of such other matters, as Collateral Agent and each Lender may reasonably deem necessary or appropriate, including, without limitation:

- (a) original Loan Documents, each duly executed by Borrower and each Subsidiary, as applicable;
- (b) subject to Section 6.6, duly executed original Control Agreements with respect to any Collateral Accounts maintained by Borrower;
- (c) duly executed original Secured Promissory Notes in favor of each Lender according to its Term A Loan Commitment Percentage;
- (d) to the extent such Shares are certificated, the certificates for the Shares, together with Assignment(s) Separate from Certificate, duly executed in blank;
- (e) the Operating Documents and good standing certificates of Borrower and its Subsidiaries certified by the Secretary of State (or equivalent agency) of Borrower's and such Subsidiaries' jurisdiction of organization or formation and each jurisdiction in which Borrower and each Subsidiary is qualified to conduct business, each as of a date no earlier than thirty (30) days prior to the Effective Date;
- (f) a completed Perfection Certificate for Borrower and each of its Subsidiaries;
- (g) the Annual Projections, for the current calendar year;

(h) duly executed original officer's certificate for Borrower and each Subsidiary that is a party to the Loan Documents, relating to the Operating Documents, corporate authorizations and other matters in a form reasonably acceptable to Collateral Agent and the Lenders (the "Officer's Certificate");

(i) certified copies, dated as of date no earlier than thirty (30) days prior to the Effective Date, of financing statement searches, as Collateral Agent shall request, accompanied by written evidence (including any UCC termination statements) that the Liens indicated in any such financing statements either constitute Permitted Liens or have been or, in connection with the initial Credit Extension, will be terminated or released;

(j) a duly executed legal opinion of counsel to Borrower dated as of the Effective Date;

(k) evidence reasonably satisfactory to Collateral Agent and the Lenders that the insurance policies required by Section 6.5 hereof are in full force and effect;

(l) a copy of any applicable Registration Rights Agreement or Investors' Rights Agreement and any amendments thereto;

(m) payment of the fees and Lenders' Expenses then due as specified in Section 2.5 hereof.

3.2 Conditions Precedent to all Credit Extensions. The obligation of each Lender to make each Credit Extension, including the initial Credit Extension, is subject to the following conditions precedent:

(a) receipt by Collateral Agent of an executed Disbursement Letter in the form of Exhibit B attached hereto;

(b) the representations and warranties in Section 5 hereof shall be true, accurate and complete in all material respects on the date of the Disbursement Letter and on the Funding Date of each Credit Extension; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true, accurate and complete in all material respects as of such date, and no Event of Default shall have occurred and be continuing or result from the Credit Extension. Each Credit Extension is Borrower's representation and warranty on that date that the representations and warranties in Section 5 hereof are true, accurate and complete in all material respects; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true, accurate and complete in all material respects as of such date;

(c) in such Lender's sole but reasonable discretion, there has not been any Material Adverse Change or any material adverse deviation by Borrower from the Annual Projections of Borrower presented to and accepted by Collateral Agent and each Lender;

(d) to the extent not delivered at the Effective Date, duly executed original Secured Promissory Notes and Warrants, in number, form and content acceptable to each Lender, and in favor of each Lender according to its Commitment Percentage, with respect to each Credit Extension made by such Lender after the Effective Date; and

(e) payment of the fees and Lenders' Expenses then due as specified in Section 2.5 hereof.

3.3 Covenant to Deliver. Borrower agrees to deliver to Collateral Agent and the Lenders each item required to be delivered to Collateral Agent under this Agreement as a condition precedent to any Credit Extension. Borrower expressly agrees that a Credit Extension made prior to the receipt by Collateral Agent or any Lender of any such item shall not constitute a waiver by Collateral Agent or any Lender of Borrower's obligation to deliver such item, and any such Credit Extension in the absence of a required item shall be made in each Lender's sole but reasonable discretion.

3.4 Procedures for Borrowing. Subject to the prior satisfaction of all other applicable conditions to the making of a Term Loan set forth in this Agreement, to obtain a Term Loan, Borrower shall notify the Lenders (which notice shall be irrevocable) by electronic mail, facsimile, or telephone by 2:00 p.m. Eastern time five (5) Business Days prior to the date the Term Loan is to be made. Together with any such electronic, facsimile or telephonic notification, Borrower shall deliver to the Lenders by electronic mail or facsimile a completed Disbursement Letter executed by a Responsible Officer or his or her designee. The Lenders may rely on any telephone notice given by a person whom a Lender reasonably believes is a Responsible Officer or designee. On the Funding Date, each Lender shall credit and/or transfer (as applicable) to the Designated Deposit Account, an amount equal to its Term Loan Commitment.

4. CREATION OF SECURITY INTEREST

4.1 Grant of Security Interest. Borrower hereby grants Collateral Agent, for the ratable benefit of the Lenders, to secure the payment and performance in full of all of the Obligations, a continuing security interest in, and pledges to Collateral Agent, for the ratable benefit of the Lenders, the Collateral, wherever located, whether now owned or hereafter acquired or arising, and all proceeds and products thereof. Borrower represents, warrants, and covenants that the security interest granted herein is and shall at all times continue to be a first priority perfected security interest in the Collateral, subject only to Permitted Liens that are permitted by the terms of this Agreement to have priority to Collateral Agent's Lien. If Borrower shall acquire a commercial tort claim (as defined in the Code) with a value in excess of Fifty Thousand Dollars (\$50,000), Borrower shall promptly notify Collateral Agent in a writing signed by Borrower, as the case may be, of the general details thereof (and further details as may be required by Collateral Agent) and grant to Collateral Agent, for the ratable benefit of the Lenders, in such writing a security interest therein and in the proceeds thereof, all upon the terms of this Agreement, with such writing to be in form and substance reasonably satisfactory to Collateral Agent.

If this Agreement is terminated, Collateral Agent's Lien in the Collateral shall continue until the Obligations (other than inchoate indemnity obligations) are repaid in full in cash. Upon payment in full in cash of the Obligations (other than inchoate indemnity obligations) and at such time as the Lenders' obligation to make Credit Extensions has terminated, Collateral Agent shall, at the sole cost and expense of Borrower, release its Liens in the Collateral and all rights therein shall revert to Borrower.

4.2 Authorization to File Financing Statements. Borrower hereby authorizes Collateral Agent to file financing statements or take any other action required to perfect Collateral Agent's security interests in the Collateral, without notice to Borrower, with all appropriate jurisdictions to perfect or protect Collateral Agent's interest or rights under the Loan Documents, including a notice that any disposition of the Collateral, except to the extent permitted by the terms of this Agreement, by Borrower, or any other Person, shall be deemed to violate the rights of Collateral Agent under the Code.

4.3 Pledge of Collateral. Borrower hereby pledges, assigns and grants to Collateral Agent, for the ratable benefit of the Lenders, a security interest in all the Shares, together with all proceeds and substitutions thereof, all cash, stock and other moneys and property paid thereon, all rights to subscribe for securities declared or granted in connection therewith, and all other cash and noncash proceeds of the foregoing, as security for the performance of the Obligations. On the Effective Date, or, to the extent not certificated as of the Effective Date, within ten (10) days of the certification of any Shares, the certificate or certificates for the Shares will be delivered to Collateral Agent, accompanied by an instrument of assignment duly executed in blank by Borrower. To the extent required by the terms and conditions governing the Shares, Borrower shall cause the books of each entity whose Shares are part of the Collateral and any transfer agent to reflect the pledge of the Shares. Upon the occurrence and during the continuance of an Event of Default hereunder, Collateral Agent may effect the transfer of any securities included in the Collateral (including but not limited to the Shares) into the name of Collateral Agent and cause new (as applicable) certificates representing such securities to be issued in the name of Collateral Agent or its transferee.

Borrower will execute and deliver such documents, and take or cause to be taken such actions, as Collateral Agent may reasonably request to perfect or continue the perfection of Collateral Agent's security interest in the Shares. Unless an Event of Default shall have occurred and be continuing, Borrower shall be entitled to exercise any voting rights with respect to the Shares and to give consents, waivers and ratifications in respect thereof, provided that no vote shall be cast or consent, waiver or ratification given or action taken which would be inconsistent with any of the terms of this Agreement or which would constitute or create any violation of any of such terms. All such rights to vote and give consents, waivers and ratifications shall terminate upon the occurrence and continuance of an Event of Default.

5. REPRESENTATIONS AND WARRANTIES

Borrower represents and warrants to Collateral Agent and the Lenders as follows:

5.1 Due Organization, Authorization: Power and Authority. Borrower and each of its Subsidiaries is duly existing and (to the extent such concept exists in its jurisdiction of organization) in good standing as a Registered Organization in its jurisdictions of organization or formation and Borrower and each of its Subsidiaries is qualified and licensed to do business and is in good standing in any jurisdiction in which the conduct of its businesses or its ownership of property requires that it be qualified except where the failure to do so could not reasonably be expected to have a Material Adverse Change. In connection with this Agreement, Borrower and each of its Subsidiaries has delivered to Collateral Agent a completed perfection certificate signed by an officer of Borrower or such Subsidiary (each a "**Perfection Certificate**" and collectively, the "**Perfection Certificates**"). Borrower represents and warrants that (a) Borrower and each of its Subsidiaries' exact legal name is that which is indicated on its respective Perfection Certificate and on the signature page of each Loan Document to which it is a party; (b) Borrower and each of its Subsidiaries is an organization of the type and is organized in the jurisdiction set forth on its respective Perfection Certificate; (c) each Perfection Certificate accurately sets forth each of Borrower's and its Subsidiaries' organizational identification number or accurately states that Borrower or such Subsidiary has none; (d) each Perfection Certificate accurately sets forth Borrower's and each of its Subsidiaries' place of business, or, if more than one, its chief executive office as well as Borrower's and each of its Subsidiaries' mailing address (if different than its chief executive office); (e) except as may be set forth on its Perfection Certificate, Borrower and each of its Subsidiaries (and each of its respective predecessors) have not, in the past five (5) years, changed its jurisdiction of organization, organizational structure or type, or any organizational number assigned by its jurisdiction; and (f) all other information set forth on the Perfection Certificates pertaining to Borrower and each of its Subsidiaries, is accurate and complete (it being understood and agreed that Borrower and each of its Subsidiaries may from time to time update certain information in the Perfection Certificates (including the information set forth in clause (d) above) after the Effective Date to the extent Borrower is permitted to take such action resulting in the applicable update by one or more specific provisions in this Agreement); such updated Perfection Certificates subject to the review and approval of Collateral Agent unless such facts, events or circumstances being updated first arose or occurred after the Effective Date and do not constitute a breach, default, or Event of Default under this Agreement or any other Loan Document. If Borrower or any of its Subsidiaries is not now a Registered Organization but later becomes one, Borrower shall notify Collateral Agent of such occurrence and provide Collateral Agent with such Person's organizational identification number within five (5) Business Days of receiving such organizational identification number.

The execution, delivery and performance by Borrower and each of its Subsidiaries of the Loan Documents to which it is a party have been duly authorized, and do not (i) conflict with any of Borrower's or such Subsidiaries' organizational documents, including its respective Operating Documents, (ii) contravene, conflict with, constitute a default under or violate any material Requirement of Law applicable thereto, (iii) contravene, conflict or violate any applicable order, writ, judgment, injunction, decree, determination or award of any Governmental Authority by which Borrower or such Subsidiary, or any of their property or assets may be bound or affected, (iv) require any action by, filing, registration, or qualification with, or Governmental Approval from, any Governmental Authority (except for filings with the Securities and Exchange Commission such Governmental Approvals which have already been obtained and are in full force and effect) or are being obtained pursuant to Section 6.1(b), or (v) constitute an event of default under any material agreement by which Borrower or any of such Subsidiaries, or their respective properties, is bound. Neither Borrower nor any of its Subsidiaries is in default under any agreement to which it is a party or by which it or any of its assets is bound in which such default could reasonably be expected to have a Material Adverse Change.

5.2 Collateral.

(a) Borrower and each its Subsidiaries have good title to, have rights in, and the power to transfer each item of the Collateral upon which it purports to grant a Lien under the Loan Documents, free and clear of any and all Liens except Permitted Liens, and neither Borrower nor any of its Subsidiaries have any Deposit Accounts, Securities Accounts, Commodity Accounts or other investment accounts other than the Collateral Accounts or the other investment accounts, if any, described in the Perfection Certificates delivered to Collateral Agent in connection herewith (as the same may be updated from time to time as permitted or required herein) with respect of which Borrower or such Subsidiary has given Collateral Agent notice and taken such actions as are necessary to give Collateral Agent a perfected security interest therein to the extent required pursuant to Section 6.6. The Accounts are bona fide, existing obligations of the Account Debtors.

(b) On the Effective Date, and except as disclosed on the Perfection Certificate: the Collateral (other than (1) inventory in transit, (2) mobile goods and equipment, and (3) locations with Collateral having an aggregate book value not in excess of Two Hundred Fifty Thousand Dollars (\$250,000.00)) is not in the possession of any third party bailee (such as a warehouse). None of the components of the Collateral (other than (1) inventory in transit, (2) mobile goods and equipment, and (3) locations with Collateral having an aggregate book value not in excess of Two Hundred Fifty Thousand Dollars (\$250,000.00)) shall be maintained at locations other than as disclosed in the Perfection Certificates on the Effective Date or locations permitted pursuant to Section 6.11.

(c) All unexpired Inventory is in all material respects of good quality, free from material defects, and all unexpired Inventory held out for sale is in all material respects of marketable quality.

(d) Borrower and each of its Subsidiaries is the sole owner of the Intellectual Property each respectively purports to solely own, free and clear of all Liens other than Permitted Liens. Except as noted on the Perfection Certificates or as otherwise disclosed pursuant to the terms of this Agreement (to the extent Borrower is permitted to take such action resulting in the applicable update by one or more specific provisions in this Agreement), neither Borrower nor any of its Subsidiaries is a party to, nor is bound by, any material license or other material agreement with respect to which Borrower or such Subsidiary is the licensee that (i) prohibits or otherwise restricts Borrower or its Subsidiaries from granting a security interest in Borrower's or such Subsidiaries' interest in such material license or material agreement or any other property, or (ii) for which a default under or termination of could interfere with Collateral Agent's or any Lender's right to sell any Collateral. Borrower shall promptly (and in any event within ten (10) Business Days) provide written notice to Collateral Agent and each Lender of Borrower or any of its Subsidiaries entering into or becoming bound by any license or other agreement with respect to which Borrower or any Subsidiary is the licensee (other than (x) over the counter software that is commercially available to the public, and (y) non-exclusive licenses (i) from research and development vendors, academic institutions and clinical trial sites entered into in the ordinary course of business, (ii) on a form substantially conforming with Borrower's form master services agreement, material transfer agreement, sponsored research agreement or clinical trial agreement, each as provided to Collateral Agent and each Lender entered into in the ordinary course of business, and (iii) from service providers of Borrower providing corporate sponsorship and/or promotional items, auditing and accounting services, human resources support services, non-proprietary information technology software, and market research entered into in the ordinary course of business, the principal purposes of which do not include the acquisition of licensing rights, but which contain such non-exclusive licenses merely ancillary to, and for

the limited purposes of facilitating, the principal purposes of the agreement, in each case so long as Borrower has complied with all other applicable terms of the Loan Documents applicable thereto).

5.3 Litigation. Except as disclosed (i) on the Perfection Certificates, or (ii) in accordance with Section 6.9 hereof, there are no actions, suits, investigations, or proceedings pending or, to the knowledge of the Responsible Officers, threatened in writing by or against Borrower or any of its Subsidiaries involving more than Two Hundred Fifty Thousand Dollars (\$250,000.00).

5.4 No Material Deterioration in Financial Condition; Financial Statements. All consolidated financial statements for Borrower and its Subsidiaries, delivered to Collateral Agent fairly present, in conformity with GAAP, in all material respects, the consolidated financial condition of Borrower and its Subsidiaries, and the consolidated results of operations of Borrower and its Subsidiaries (subject to year-end adjustments and the absence of footnotes) as of the dates and for the periods presented. There has not been any material deterioration in the consolidated financial condition of Borrower and its Subsidiaries since the date of the most recent financial statements submitted to any Lender.

5.5 Solvency. Borrower is Solvent, and Borrower and each of its Subsidiaries, taken as a whole, is Solvent.

5.6 Regulatory Compliance. Neither Borrower nor any of its Subsidiaries is an “investment company” or a company “controlled” by an “investment company” under the Investment Company Act of 1940, as amended. Neither Borrower nor any of its Subsidiaries is engaged as one of its important activities in extending credit for margin stock (under Regulations X, T and U of the Federal Reserve Board of Governors). Borrower and each of its Subsidiaries has complied in all material respects with the Federal Fair Labor Standards Act. Neither Borrower nor any of its Subsidiaries is a “holding company” or an “affiliate” of a “holding company” or a “subsidiary company” of a “holding company” as each term is defined and used in the Public Utility Holding Company Act of 2005. Neither Borrower nor any of its Subsidiaries has violated any laws, ordinances or rules, the violation of which could reasonably be expected to have a Material Adverse Change. Neither Borrower’s nor any of its Subsidiaries’ properties or assets has been used by Borrower or such Subsidiary or, to Borrower’s knowledge, by previous Persons, in disposing, producing, storing, treating, or transporting any hazardous substance other than in material compliance with applicable laws. Borrower and each of its Subsidiaries has obtained all consents, approvals and authorizations of, made all declarations or filings with, and given all notices to, all Governmental Authorities that are necessary to continue their respective businesses as currently conducted.

None of Borrower, any of its Subsidiaries, or any of Borrower’s or its Subsidiaries’ Affiliates or any of their respective agents acting or benefiting in any capacity in connection with the transactions contemplated by this Agreement is (i) in violation of any Anti-Terrorism Law, (ii) engaging in or conspiring to engage in any transaction that evades or avoids, or has the purpose of evading or avoiding or attempts to violate, any of the prohibitions set forth in any Anti-Terrorism Law, or (iii) is a Blocked Person. None of Borrower, any of its Subsidiaries, or to the knowledge of Borrower and any of their Affiliates or agents, acting or benefiting in any capacity in connection with the transactions contemplated by this Agreement, (x) conducts any business or engages in making or receiving any contribution of funds, goods or services to or for the benefit of any Blocked Person, or (y) deals in, or otherwise engages in any transaction relating to, any property or interest in property blocked pursuant to Executive Order No. 13224, any similar executive order or other Anti-Terrorism Law.

5.7 Investments. Neither Borrower nor any of its Subsidiaries owns any stock, shares, partnership interests or other equity securities except for Permitted Investments.

5.8 Tax Returns and Payments; Pension Contributions. Borrower and each of its Subsidiaries has timely filed or have timely obtained extensions for filing all required tax returns and reports, and Borrower and each of its Subsidiaries, has timely paid all foreign, federal, state, and local taxes, assessments, deposits and contributions owed by Borrower and such Subsidiaries, in all jurisdictions in which Borrower or any such Subsidiary is subject to taxes, including the United States, unless (a) such taxes are being contested in accordance with the following sentence or (b) in the case of foreign, state or local taxes, if such foreign, state or local taxes, assessments, deposits and contributions do not, individually or in the aggregate, exceed Seventy-Five Thousand Dollars (\$75,000.00). Borrower and each of its Subsidiaries, may defer payment of any contested taxes, provided that Borrower or such Subsidiary, (a) in good faith contests its obligation to pay the taxes by appropriate proceedings promptly and diligently instituted and conducted, (b) notifies Collateral Agent in writing of the commencement of, and any

material development in, the proceedings, and (c) posts bonds or takes any other steps required to prevent the Governmental Authority levying such contested taxes from obtaining a Lien upon any of the Collateral that is other than a “**Permitted Lien**.” Neither Borrower nor any of its Subsidiaries is aware of any claims or adjustments proposed for any of Borrower’s or such Subsidiaries’, prior tax years which could result in additional taxes becoming due and payable by Borrower or its Subsidiaries in excess of Seventy-Five Thousand Dollars (\$75,000.00), except to the extent that such taxes are being contested in accordance with the immediately preceding sentence. Borrower and each of its Subsidiaries have paid all amounts necessary to fund all present pension, profit sharing and deferred compensation plans in accordance with their terms, and neither Borrower nor any of its Subsidiaries have, withdrawn from participation in, and have not permitted partial or complete termination of, or permitted the occurrence of any other event with respect to, any such plan which could reasonably be expected to result in any liability of Borrower or its Subsidiaries, including any liability to the Pension Benefit Guaranty Corporation or its successors or any other Governmental Authority.

5.9 Use of Proceeds. Borrower shall use the proceeds of the Credit Extensions solely as working capital and to fund its general business requirements in accordance with the provisions of this Agreement, and not for personal, family, household or agricultural purposes.

5.10 Shares. Borrower has full power and authority to create a first lien on the Shares and no disability or contractual obligation exists that would prohibit Borrower from pledging the Shares pursuant to this Agreement. To Borrower’s knowledge, there are no subscriptions, warrants, rights of first refusal or other restrictions on transfer relative to, or options exercisable with respect to the Shares. The Shares have been and will be duly authorized and validly issued, and are fully paid and non-assessable. To Borrower’s knowledge, the Shares are not the subject of any present or threatened suit, action, arbitration, administrative or other proceeding, and Borrower knows of no reasonable grounds for the institution of any such proceedings.

5.11 Full Disclosure. No written representation, warranty or other statement of Borrower or any of its Subsidiaries in any certificate or written statement given to Collateral Agent or any Lender, as of the date such representation, warranty, or other statement was made, taken together with all such written certificates and written statements given to Collateral Agent or any Lender, contains any untrue statement of a material fact or omits to state a material fact necessary to make the statements contained in the certificates or statements not misleading in light of the circumstances under which they were made (it being recognized that the projections and forecasts provided by Borrower in good faith and based upon reasonable assumptions are not viewed as facts and that actual results during the period or periods covered by such projections and forecasts may differ from the projected or forecasted results).

5.12 Definition of “Knowledge.” For purposes of the Loan Documents, whenever a representation or warranty is made to Borrower’s knowledge or awareness, to the “best of” Borrower’s knowledge, or with a similar qualification, knowledge or awareness means the actual knowledge, after reasonable investigation, of the Responsible Officers.

6. AFFIRMATIVE COVENANTS

Borrower shall, and shall cause each of its Subsidiaries to, do all of the following:

6.1 Government Compliance.

(a) Maintain its and all its Subsidiaries’ legal existence and good standing (to the extent such concept exists in the relevant jurisdiction of organization) in their respective jurisdictions of organization and maintain qualification in each jurisdiction in which the failure to so qualify could reasonably be expected to have a Material Adverse Change. Comply with all laws, ordinances and regulations to which Borrower or any of its Subsidiaries is subject, the noncompliance with which could reasonably be expected to have a Material Adverse Change.

(b) Obtain and keep in full force and effect, all of the material Governmental Approvals necessary for the performance by Borrower and its Subsidiaries of their respective businesses and obligations under the Loan Documents and the grant of a security interest to Collateral Agent for the ratable benefit of the Lenders, in all of the Collateral. Borrower shall promptly provide copies to Collateral Agent of any material Governmental Approvals obtained by Borrower or any of its Subsidiaries.

6.2 Financial Statements, Reports, Certificates.

(a) Deliver to each Lender:

(i) as soon as available, but no later than (x) thirty (30) days after the last day of each month which is not the last month of a fiscal quarter of Borrower, and (y) forty-five (45) days after the last day of each month which is the last month of a fiscal quarter of Borrower, a company prepared consolidated and consolidating (if prepared) balance sheet, income statement and cash flow statement covering the consolidated operations of Borrower and its Subsidiaries for such month certified by a Responsible Officer and in a form reasonably acceptable to Collateral Agent;

(ii) as soon as available, but no later than the earlier of (A) one hundred twenty (120) days after the last day of Borrower's fiscal year or (B) within five (5) days of filing with the SEC, audited consolidated financial statements prepared under GAAP, consistently applied, together with an unqualified (other than going concern qualifications with respect to the maturity of any outstanding Term Loans within the next year or explanatory language as it relates to Borrower's cash levels) opinion on the financial statements from Ernst & Young LLP or another independent certified public accounting firm acceptable to Collateral Agent in its reasonable discretion;

(iii) as soon as available after approval thereof by Borrower's Board of Directors, but no later than sixty (60) days after the last day of each of Borrower's fiscal years, Borrower's annual financial projections for the entire current fiscal year as approved by Borrower's Board of Directors, which such annual financial projections shall include management prepared (which shall be reviewed by Borrower's chief financial officer, but need not be approved by Borrower's Board of Directors) quarterly cash runway projections (such annual financial projections as originally delivered to Collateral Agent and the Lenders are referred to herein as the "**Annual Projections**"); provided that, any (x) revisions of the Annual Projections approved by Borrower's Board of Directors shall be promptly delivered to Collateral Agent and the Lenders but in any event no later than ten (10) Business Days after such approval and (y) material revisions of the management prepared Annual Projections shall be promptly delivered to Collateral Agent and the Lenders but in any event no later than ten (10) Business Days after such revisions are reviewed by Borrower's chief financial officer;

(iv) within five (5) Business Days of delivery, copies of all statements, reports and notices made available to Borrower's security holders or holders of Subordinated Debt;

(v) within five (5) Business Days after filing, all reports on Form 10-K, 10-Q and 8-K filed with the Securities and Exchange Commission,

(vi) prompt notice of any amendments of or other changes to (x) the Operating Documents of Borrower or any of its Subsidiaries, or (y) in the event that Borrower is no longer subject to the reporting requirements under the Securities Exchange Act of 1934, as amended, prompt notice of any material change to the capitalization of Borrower together, in each case, together with any copies reflecting such amendments or changes with respect thereto;

(vii) prompt notice of any event that could reasonably be expected to materially and adversely affect the value of the Intellectual Property;

(viii) as soon as available, but no later than (x) thirty (30) days after the last day of each month which is not the last month of a fiscal quarter of Borrower, and (y) forty-five (45) days after the last day of each month which is the last month of a fiscal quarter of Borrower, copies of the month-end account statements for each Collateral Account maintained by Borrower or its Subsidiaries, which statements may be provided to Collateral Agent and each Lender by Borrower or directly from the applicable institution(s), and

- (ix) other information as reasonably requested by Collateral Agent or any Lender.

Notwithstanding the foregoing, documents required to be delivered pursuant to the terms hereof (to the extent any such documents are included in materials otherwise filed with the Securities and Exchange Commission) may be delivered electronically and if so delivered, shall be deemed to have been delivered on the date (i) on which Borrower posts such documents, or provides a link thereto, on Borrower's website on the internet at Borrower's website address or (ii) on which such documents are posted on Borrower's behalf on the website of the Securities and Exchange Commission.

(b) Concurrently with the delivery of the financial statements specified in Section 6.2(a)(i) above but no later than (x) thirty (30) days after the last day of each month which is not the last month of a fiscal quarter of Borrower, and (y) forty-five (45) days after the last day of each month which is the last month of a fiscal quarter, deliver to each Lender, a duly completed Compliance Certificate signed by a Responsible Officer.

(c) Keep proper books of record and account in accordance with GAAP in all material respects, in which full, true and correct entries shall be made of all dealings and transactions in relation to its business and activities. Borrower shall, and shall cause each of its Subsidiaries to, allow, at the sole cost of Borrower, Collateral Agent or any Lender, during regular business hours upon reasonable prior notice (provided that no notice shall be required when an Event of Default has occurred and is continuing), to visit and inspect any of its properties, to examine and make abstracts or copies from any of its books and records, and to conduct a collateral audit and analysis of its operations and the Collateral. Such audits shall be conducted no more often than twice every year unless (and more frequently if) an Event of Default has occurred and is continuing.

6.3 Inventory; Returns. Keep all unexpired Inventory in all material respects in good condition, free from material defects, and keep all unexpired Inventory held out for sale in all material respects in marketable condition. Returns and allowances between Borrower, or any of its Subsidiaries, and their respective Account Debtors shall follow Borrower's, or such Subsidiary's, customary practices as they exist at the Effective Date. Borrower must promptly notify Collateral Agent and the Lenders of all returns, recoveries, disputes and claims that involve Inventory with a book value of more than Two Hundred Fifty Thousand Dollars (\$250,000.00) individually or in the aggregate in any calendar year.

6.4 Taxes; Pensions. Timely file or obtain extensions for filing and require each of its Subsidiaries to timely file, all required tax returns and reports and timely pay, and require each of its Subsidiaries to timely file, all foreign, federal, state, and local taxes, assessments, deposits and contributions owed by Borrower or its Subsidiaries, except for deferred payment of any taxes contested pursuant to the terms of Section 5.8 hereof and in the case of foreign, state or local taxes, if such foreign, state or local taxes, assessments, deposits and contributions do not, individually or in the aggregate, exceed Seventy-Five Thousand Dollars (\$75,000.00), and shall deliver to Collateral Agent, on demand, appropriate certificates attesting to such payments, and pay all amounts necessary to fund all present pension, profit sharing and deferred compensation plans in accordance with the terms of such plans.

6.5 Insurance. Keep Borrower's and its Subsidiaries' business and the Collateral insured for risks and in amounts standard for companies in Borrower's and its Subsidiaries' industry and location and as Collateral Agent may reasonably request. Insurance policies shall be in a form, with companies, and in amounts that are reasonably satisfactory to Collateral Agent and Lenders. All property policies shall have a lender's loss payable endorsement showing Collateral Agent as lender loss payee and waive subrogation against Collateral Agent, and all liability policies shall show, or have endorsements showing, Collateral Agent, as additional insured. The Collateral Agent shall be named as lender loss payee and/or additional insured with respect to any such insurance providing coverage in respect of any Collateral, and each provider of any such insurance shall agree, by endorsement upon the policy or policies issued by it or by independent instruments furnished to the Collateral Agent, that it will give the Collateral Agent thirty (30) days (or, ten (10) Business Days, in the event of cancellation for non-payment of premiums) prior written notice before any such policy or policies shall be canceled. At Collateral Agent's request, Borrower shall deliver certified copies of policies and evidence of all premium payments. Proceeds payable under any policy shall, at Collateral Agent's option, be payable to Collateral Agent, for the ratable benefit of the Lenders, on account of the Obligations. Notwithstanding the foregoing, (a) so long as no Event of Default has occurred and is continuing, Borrower shall have the option of applying the proceeds of any casualty policy up to Five Hundred Thousand Dollars (\$500,000.00) with respect to any loss, but not exceeding Five Hundred Thousand Dollars (\$500,000.00), in the aggregate for all losses under all casualty policies in any one year, toward the replacement or repair of destroyed

or damaged property; provided that any such replaced or repaired property (i) shall be of better, equal or like value as the replaced or repaired Collateral and (ii) shall be deemed Collateral in which Collateral Agent has been granted a first priority security interest, and (b) after the occurrence and during the continuance of an Event of Default, all proceeds payable under such casualty policy shall, at the option of Collateral Agent, be payable to Collateral Agent, for the ratable benefit of the Lenders, on account of the Obligations. If Borrower or any of its Subsidiaries fails to obtain insurance as required under this Section 6.5 or to pay any amount or furnish any required proof of payment to third persons, Collateral Agent and/or any Lender may make, at Borrower's expense, all or part of such payment or obtain such insurance policies required in this Section 6.5, and take any action under the policies Collateral Agent or such Lender deems prudent.

6.6 Bank Accounts.

(a) Maintain all of Borrower's and its Subsidiaries' Collateral Accounts (other than the Excluded Accounts) in accounts which are subject to a Control Agreement in favor of Collateral Agent.

(b) Borrower shall provide Collateral Agent five (5) days' prior written notice before Borrower or any of its Subsidiaries establishes any Collateral Account (other than the Excluded Accounts) at or with any Person other than as disclosed in the Perfection Certificate delivered on the Effective Date. In addition, for each Collateral Account that Borrower or any Guarantor at any time maintains, Borrower or such Guarantor shall cause the applicable bank or financial institution at or with which such Collateral Account is maintained to execute and deliver a Control Agreement or other appropriate instrument with respect to such Collateral Account to perfect Collateral Agent's Lien in such Collateral Account in accordance with the terms hereunder prior to the establishment of such Collateral Account, which Control Agreement may not be terminated without prior written consent of Collateral Agent. The provisions of the previous sentence shall not apply to (i) Collateral Accounts exclusively used for payroll, payroll taxes and other employee wage and benefit payments to or for the benefit of Borrower's, or any of its Subsidiaries', employees; (ii) any Collateral Accounts of Syros Securities, and (iii) Collateral Accounts subject to a lien permitted by clauses (j) and (l) of "Permitted Liens" for all such Accounts at any time ((i) through (iii) collectively, the "Excluded Accounts").

(c) Neither Borrower nor any of its Subsidiaries shall maintain any Collateral Accounts except Collateral Accounts maintained in accordance with Sections 6.6(a) and (b).

6.7 Protection of Intellectual Property Rights. Borrower and each of its Subsidiaries shall: (a) use commercially reasonable efforts to protect, defend and maintain the validity and enforceability of its Intellectual Property that is material to Borrower's business; (b) promptly advise Collateral Agent in writing upon becoming aware of any material infringement by a third party of its Intellectual Property; and (c) not allow any Intellectual Property material to Borrower's business to be abandoned forfeited or dedicated to the public without Collateral Agent's prior written consent.

6.8 Litigation Cooperation. Commencing on the Effective Date and continuing through the termination of this Agreement, make available to Collateral Agent and the Lenders, at reasonable times and upon reasonable notice, without expense to Collateral Agent or the Lenders, Borrower and each of Borrower's officers, employees and agents and Borrower's Books, to the extent that Collateral Agent or any Lender may reasonably deem them necessary to prosecute or defend any third-party suit or proceeding instituted by or against Collateral Agent or any Lender with respect to any Collateral or relating to Borrower.

6.9 Notices of Litigation and Default. Borrower will give prompt written notice to Collateral Agent and the Lenders of any litigation or governmental proceedings pending or threatened (in writing) against Borrower or any of its Subsidiaries, which could reasonably be expected to result in damages or costs to Borrower or any of its Subsidiaries of Two Hundred Fifty Thousand Dollars (\$250,000.00) or more or which could reasonably be expected to have a Material Adverse Change. Without limiting or contradicting any other more specific provision of this Agreement, promptly (and in any event within three (3) Business Days) upon Borrower becoming aware of the existence of any Event of Default or event which, with the giving of notice or passage of time, or both, would constitute an Event of Default, Borrower shall give written notice to Collateral Agent and the Lenders of such occurrence, which such notice shall include a reasonably detailed description of such Event of Default or event which, with the giving of notice or passage of time, or both, would constitute an Event of Default.

6.10 MSC Investment Condition. Borrower shall maintain unrestricted cash balance in one or more Control Accounts subject to Control Agreements in favor of Collateral Agent in an aggregate amount of not less than an amount equal to the lesser of (i) One Hundred Ten percent (110.00%) of the aggregate principal amount of outstanding Obligations and (ii) the amount of Borrower's and all of its Subsidiaries' (including Syros Securities) aggregate consolidated cash and Cash Equivalent assets (the "MSC Investment Condition").

6.11 Landlord Waivers; Bailee Waivers. In the event that Borrower or any of its Subsidiaries, after the Effective Date, (a) leases any new offices or business locations, including warehouses, and such new location is either (x) the chief executive office of the Borrower or such Subsidiary or (y) the Collateral at any such new location has a book value in excess of Two Hundred Fifty Thousand (\$250,000.00) in the aggregate, Borrower shall cause the landlord of such property to execute and deliver a landlord waiver in form and substance reasonably satisfactory to Collateral Agent, or (b) stores any portion of the Collateral with, or delivers any portion of such Collateral to, a bailee, and the Collateral at such new location has a book value in excess of Two Hundred Fifty Thousand (\$250,000.00) in the aggregate, Borrower shall cause the bailee of such property to execute and deliver a bailee waiver in form and substance reasonably satisfactory to Collateral Agent.

6.12 Creation/Acquisition of Subsidiaries. In the event Borrower, or any of its Subsidiaries creates or acquires any Subsidiary after the Effective Date, Borrower shall provide prior written notice to Collateral Agent and each Lender of the creation or acquisition of such new Subsidiary and take all such action as may be reasonably required by Collateral Agent or any Lender to cause each such Subsidiary to become a co-Borrower hereunder or to guarantee the Obligations of Borrower under the Loan Documents and, in each case, grant a continuing pledge and security interest in and to the assets of such Subsidiary (substantially as described on Exhibit A hereto); and Borrower (or its Subsidiary, as applicable) shall grant and pledge to Collateral Agent, for the ratable benefit of the Lenders, a perfected security interest in the Shares of each such newly created Subsidiary.

6.13 Further Assurances.

(a) Execute any further instruments and take further action as Collateral Agent or any Lender reasonably requests to perfect or continue Collateral Agent's Lien in the Collateral or to effect the purposes of this Agreement.

(b) Deliver to Collateral Agent and Lenders, within five (5) days after the same are sent or received, copies of all material correspondence, reports, documents and other filings with any Governmental Authority that could reasonably be expected to have a material adverse effect on any of the Governmental Approvals material to Borrower's business or otherwise could reasonably be expected to have a Material Adverse Change.

7. NEGATIVE COVENANTS

Borrower shall not, and shall not permit any of its Subsidiaries to, do any of the following without the prior written consent of the Required Lenders:

7.1 Dispositions. Convey, sell, lease, transfer, assign, or otherwise dispose of (collectively, "**Transfer**"), or permit any of its Subsidiaries to Transfer, all or any part of its business or property, except for Transfers (a) of Inventory in the ordinary course of business; (b) of worn out, surplus or obsolete Equipment; (c) in connection with Permitted Liens, Permitted Investments and Permitted Licenses; (d) from any Subsidiary of Borrower to Borrower or between Loan Parties; (e) of cash and Cash Equivalents (i) in connection with transactions in the ordinary course of business and (ii) in connection with transactions that (A) are approved by Borrower's board of directors (to the extent Board approval is required by Borrower's policies or other organizational documents), (B) are customary for the Borrower's industry and (C) not otherwise prohibited hereunder; (f) mandated destruction of such Pre-Clinical and Clinical Trial Supplies and (h) other Transfers of property, other than Intellectual Property, having a book value not exceeding Two Hundred Fifty Thousand Dollars (\$250,000.00) in the aggregate during any fiscal year.

7.2 Changes in Business, Management, Ownership, or Business Locations. (a) Engage in or permit any of its Subsidiaries to engage in any business other than the businesses engaged in by Borrower as of the Effective Date or reasonably related or incidental thereto; (b) liquidate or dissolve; or (c) (i) any Key Person shall cease to be actively engaged in the management of Borrower unless written notice thereof is promptly provided to Collateral Agent, but in no event later than ten (10) Business Days, or (ii) (x) enter into, other than as expressly permitted by

the last sentence in Section 7.3, or (y) consummate, any transaction or series of related transactions in which the stockholders of Borrower who were not stockholders immediately prior to the first such transaction own more than forty nine percent (49%) of the voting power of Borrower immediately after giving effect to such transaction or related series of such transactions (other than by the sale of Borrower's equity securities in a public offering, a private placement of equity or to venture capital or institutional investors so long as Borrower identifies to Collateral Agent the venture capital or institutional investors prior to the closing of the transaction) (any such transaction, a "**Change in Control**"). Borrower shall not, without at least ten (10) days' prior written notice to Collateral Agent: (A) add any new offices or business locations, including warehouses, except in accordance with the provisions of Section 6.11; (B) change its jurisdiction of organization, (C) change its organizational structure or type, (D) change its legal name, or (E) change any organizational number (if any) assigned by its jurisdiction of organization.

7.3 Mergers or Acquisitions. Merge or consolidate, or permit any of its Subsidiaries to merge or consolidate, with any other Person, or acquire, or permit any of its Subsidiaries to acquire, all or substantially all of the capital stock, shares or property of another Person, other than Permitted Acquisitions. A Subsidiary may merge or consolidate into another Subsidiary (provided such surviving Subsidiary is a Loan Party hereunder) or with (or into) Borrower provided Borrower is the surviving legal entity, and as long as no Event of Default is occurring prior thereto or arises as a result thereof. Without limiting the foregoing, Borrower shall not, without Collateral Agent's prior written consent, enter into any binding contractual arrangement with (a) any Person that would result in a Change in Control, unless (i) no Event of Default exists when such agreement is entered into by Borrower, (ii) such agreement does not give such Person the right to claim any fees, payments or damages from Borrower in excess of Five Hundred Thousand Dollars (\$500,000.00), (iii) such contractual arrangement provides that the Obligations hereunder will be repaid in full in cash upon consummation of the Change of Control, and (iv) Borrower notifies Collateral Agent in advance of entering into such an agreement, or (b) an investment bank providing for a specific mandate to attempt to facilitate a Change in Control unless (i) no Event of Default exists when such agreement is entered into by Borrower, (ii) such agreement does not give such Person a retainer or any other fee payable by Borrower whether or not a transaction is consummated in excess of Five Hundred Thousand Dollars (\$500,000.00), and (iii) Borrower notifies Collateral Agent in advance of entering into such an agreement; provided, however, so long as no Event of Default exists when such agreement is entered into by Borrower, a binding contractual arrangement with an investment bank providing for a general strategic review mandate shall not be prohibited under this clause (b) unless and until such bank is provided a specific mandate to attempt to facilitate a Change in Control, in which case clause (b) above shall apply.

7.4 Indebtedness. Create, incur, assume, or be liable for any Indebtedness, or permit any Subsidiary to do so, other than Permitted Indebtedness.

7.5 Encumbrance. (i) Create, incur, allow, or suffer any Lien on any of its property, or assign or convey any right to receive income, including the sale of any Accounts, or permit any of its Subsidiaries to do so, except for Permitted Liens, or (ii) permit any Collateral not to be subject to the first priority security interest granted herein (except for Permitted Liens that are permitted by the terms of this Agreement to have priority over Collateral Agent's or any Lender's Lien), or enter into any agreement, document, instrument or other arrangement (except with or in favor of Collateral Agent, for the ratable benefit of the Lenders) with any Person which directly or indirectly prohibits or has the effect of prohibiting Borrower, or any of its Subsidiaries, from assigning, mortgaging, pledging, granting a security interest in or upon, or encumbering any of Borrower's or such Subsidiary's Intellectual Property, except (i) as permitted in Section 7.1 hereof, and (ii) in connection with Permitted Liens herein.

7.6 Maintenance of Collateral Accounts. Maintain any Collateral Account except pursuant to the terms of Section 6.6 hereof.

7.7 Distributions; Investments. (a) Pay any dividends (other than (i) dividends payable solely in capital stock and (ii) dividends by any Subsidiary of Borrower to Borrower) or make any distribution or payment in respect of or redeem, retire or purchase any capital stock (except that Borrower or any Subsidiary may (i) repurchase the stock of current or former employees, directors or consultants pursuant to stock repurchase agreements by the cancellation of indebtedness owed by such former employees regardless of whether an Event of Default exists, (ii) convert any of its convertible securities into other securities pursuant to the terms of such convertible securities or otherwise in exchange thereof, (iii) pay de minimis amounts of cash in lieu of fractional shares upon conversion of convertible securities or upon any stock split or consolidation, provided such cash amounts do not exceed Two Hundred Fifty Thousand Dollars (\$250,000.00) in the aggregate per fiscal year, (iv) make purchases of capital stock or options to acquire such capital stock with the proceeds received from a substantially concurrent issuance of

capital stock or convertible securities, provided such repurchases do not exceed Two Hundred Fifty Thousand Dollars (\$250,000.00) in the aggregate per fiscal year; (v) make purchases of capital stock in connection with (1) the exercise of stock options or stock appreciation rights or (2) the satisfaction of withholding tax obligations; in each case, by way of cashless (or, “net”) exercise; or (vi) make repurchases pursuant to the terms of employee stock purchase plans, employee restricted stock agreements, stockholder rights plans, director or consultant stock option plans, or similar plans, provided such repurchases do not exceed Two Hundred Fifty Thousand Dollars (\$250,000.00) in the aggregate per fiscal year) or (b) directly or indirectly make any Investment other than Permitted Investments, or permit any of its Subsidiaries to make any Investment other than Permitted Investments.

7.8 Transactions with Affiliates. Directly or indirectly enter into or permit to exist any material transaction with any Affiliate of Borrower or any of its Subsidiaries, except for (a) transactions that are in the ordinary course of Borrower’s or such Subsidiary’s business, upon fair and reasonable terms that are no less favorable to Borrower or such Subsidiary than would be obtained in an arm’s length transaction with a non-affiliated Person, (b) transactions constituting bona fide Subordinated Debt or equity financings for capital raising purposes by Borrower’s investors, (c) reasonable and customary compensation and benefit arrangements (including the granting of options or other equity compensation arrangements) and any indemnification arrangements with employees, officers, directors or consultants entered into in the ordinary course of business and approved by such Loan Party’s Board to the extent required by such Loan Party’s organizational documents, and (d) transactions permitted by clauses (f) and (g) of the definition of “Permitted Investments”.

7.9 Subordinated Debt. (a) Make or permit any payment on any Subordinated Debt, except under the terms of the subordination, intercreditor, or other similar agreement to which such Subordinated Debt is subject, or (b) amend any provision in any document relating to the Subordinated Debt which would increase the amount thereof, except to the extent expressly permitted under the terms of the subordination, intercreditor, or other similar agreement to which such Subordinated Debt is subject, or adversely affect the subordination thereof to Obligations owed to the Lenders.

7.10 Compliance. Become an “investment company” or a company controlled by an “investment company”, under the Investment Company Act of 1940, as amended, or undertake as one of its important activities extending credit to purchase or carry margin stock (as defined in Regulation U of the Board of Governors of the Federal Reserve System), or use the proceeds of any Credit Extension for that purpose; fail to meet the minimum funding requirements of ERISA, permit a Reportable Event or Prohibited Transaction, as defined in ERISA, to occur; fail to comply with the Federal Fair Labor Standards Act or violate any other law or regulation, if the violation could reasonably be expected to have a Material Adverse Change, or permit any of its Subsidiaries to do so; withdraw or permit any Subsidiary to withdraw from participation in, permit partial or complete termination of, or permit the occurrence of any other event with respect to, any present pension, profit sharing and deferred compensation plan which could reasonably be expected to result in any liability of Borrower or any of its Subsidiaries, including any such liability to the Pension Benefit Guaranty Corporation or its successors or any other Governmental Authority.

7.11 Compliance with Anti-Terrorism Laws. Collateral Agent hereby notifies Borrower and each of its Subsidiaries that pursuant to the requirements of Anti-Terrorism Laws, and Collateral Agent’s policies and practices, Collateral Agent is required to obtain, verify and record certain information and documentation that identifies Borrower and each of its Subsidiaries and their principals, which information includes the name and address of Borrower and each of its Subsidiaries and their principals and such other information that will allow Collateral Agent to identify such party in accordance with Anti-Terrorism Laws. Neither Borrower nor any of its Subsidiaries shall, nor shall Borrower or any of its Subsidiaries permit any Affiliate to, directly or indirectly, knowingly enter into any documents, instruments, agreements or contracts with any Person listed on the OFAC Lists. Borrower and each of its Subsidiaries shall immediately notify Collateral Agent if Borrower or such Subsidiary has knowledge that Borrower, or any Subsidiary or Affiliate of Borrower, is listed on the OFAC Lists or (a) is convicted on, (b) pleads *nolo contendere* to, (c) is indicted on, or (d) is arraigned and held over on charges involving money laundering or predicate crimes to money laundering. Neither Borrower nor any of its Subsidiaries shall, nor shall Borrower or any of its Subsidiaries, permit any Affiliate to, directly or indirectly, (i) conduct any business or engage in any transaction or dealing with any Blocked Person, including, without limitation, the making or receiving of any contribution of funds, goods or services to or for the benefit of any Blocked Person, (ii) deal in, or otherwise engage in any transaction relating to, any property or interests in property blocked pursuant to Executive Order No. 13224 or any similar executive order or other Anti-Terrorism Law, or (iii) engage in or

conspire to engage in any transaction that evades or avoids, or has the purpose of evading or avoiding, or attempts to violate, any of the prohibitions set forth in Executive Order No. 13224 or other Anti-Terrorism Law.

7.12 Assets in Syros Ireland. Transfer to, license to or permit Syros Ireland to hold or maintain, at any time prior to Syros Ireland becoming a Borrower hereunder, (a) any Intellectual Property or (b) any other assets having an aggregate value in excess of One Hundred Thousand Dollars (\$100,000.00).

8. EVENTS OF DEFAULT

Any one of the following shall constitute an event of default (an “**Event of Default**”) under this Agreement:

8.1 Payment Default. Borrower fails to (a) make any payment of principal or interest on any Credit Extension on its due date, or (b) pay any other Obligations within three (3) Business Days after such Obligations are due and payable (which three (3) Business Day grace period shall not apply to payments due on the Maturity Date or the date of acceleration pursuant to Section 9.1 (a) hereof). During the cure period, the failure to cure the payment default is not an Event of Default (but no Credit Extension will be made during the cure period);

8.2 Covenant Default.

(a) Borrower or any of its Subsidiaries fails or neglects to perform any obligation in Sections 6.2 (Financial Statements, Reports, Certificates), 6.4 (Taxes), 6.5 (Insurance), 6.6 (Bank Accounts), 6.7 (Protection of Intellectual Property Rights), 6.9 (Notice of Litigation and Default), 6.10 (Financial Covenant), 6.11 (Landlord Waivers; Bailee Waivers), or 6.12 (Creation/Acquisition of Subsidiaries) or Borrower violates any covenant in Section 7; or

(b) Borrower, or any of its Subsidiaries, fails or neglects to perform, keep, or observe any other term, provision, condition, covenant or agreement contained in this Agreement or any Loan Documents, and as to any default (other than those specified in this Section 8) under such other term, provision, condition, covenant or agreement that can be cured, has failed to cure the default within ten (10) days after the occurrence thereof; provided, however, that if the default cannot by its nature be cured within the ten (10) day period or cannot after diligent attempts by Borrower be cured within such ten (10) day period, and such default is likely to be cured within a reasonable time, then Borrower shall have an additional period (which shall not in any case exceed thirty (30) days) to attempt to cure such default, and within such reasonable time period the failure to cure the default shall not be deemed an Event of Default (but no Credit Extensions shall be made during such cure period). Grace periods provided under this Section shall not apply, among other things, to financial covenants or any other covenants set forth in subsection (a) above;

8.3 Material Adverse Change. A Material Adverse Change occurs;

8.4 Attachment; Levy; Restraint on Business.

(a) (i) The service of process seeking to attach, by trustee or similar process, any funds of Borrower or any of its Subsidiaries or of any entity under control of Borrower or its Subsidiaries on deposit with any Lender or any Lender's Affiliate or any bank or other institution at which Borrower or any of its Subsidiaries maintains a Collateral Account, or (ii) a notice of lien, levy, or assessment is filed against Borrower or any of its Subsidiaries or their respective assets by any government agency, and the same under subclauses (i) and (ii) hereof are not, within ten (10) days after the occurrence thereof, discharged or stayed (whether through the posting of a bond or otherwise); provided, however, no Credit Extensions shall be made during any ten (10) day cure period; and

(b) (i) any material portion of Borrower's or any of its Subsidiaries' assets is attached, seized, levied on, or comes into possession of a trustee or receiver, or (ii) any court order enjoins, restrains, or prevents Borrower or any of its Subsidiaries from conducting any part of its business;

8.5 Insolvency. (a) Borrower or any of its Subsidiaries is or becomes Insolvent; (b) Borrower or any of its Subsidiaries begins an Insolvency Proceeding; or (c) an Insolvency Proceeding is begun against Borrower or any of its Subsidiaries and not dismissed or stayed within forty-five (45) days (but no Credit Extensions shall be made while Borrower or any Subsidiary is Insolvent and/or until any Insolvency Proceeding is dismissed);

8.6 Other Agreements. There is a default in any agreement to which Borrower or any of its Subsidiaries is a party with a third party or parties resulting in a right by such third party or parties, whether or not exercised, to accelerate the maturity of any Indebtedness in an amount in excess of Two Hundred Fifty Thousand Dollars (\$250,000.00) or that could reasonably be expected to have a Material Adverse Change; provided, however, that the Event of Default under this Section 8.6 caused by the occurrence of a breach or default under such other agreement shall be cured or waived for purposes of this Agreement upon Collateral Agent receiving written notice from the party asserting such breach or default of such cure or waiver of the breach or default under such other agreement, if at the time of such cure or waiver under such other agreement (x) Collateral Agent or any Lender has not declared an Event of Default under this Agreement and/or exercised any rights with respect thereto; (y) any such cure or waiver does not result in an Event of Default under any other provision of this Agreement or any Loan Document; and (z) in connection with any such cure or waiver under such other agreement, the terms of any agreement with such third party are not modified or amended in any manner which could in the good faith business judgment of Collateral Agent or Lenders to be materially less advantageous to Borrower;

8.7 Judgments. One or more final judgments, orders, or decrees for the payment of money in an amount, individually or in the aggregate, of at least Two Hundred Fifty Thousand Dollars (\$250,000.00) (not covered by independent third-party insurance as to which liability has been accepted by such insurance carrier) shall be rendered against Borrower or any of its Subsidiaries and shall remain unsatisfied, unvacated, or unstayed for a period of twenty (20) days after the entry thereof (provided that no Credit Extensions will be made prior to the satisfaction, vacation, or stay of such judgment, order or decree);

8.8 Misrepresentations. Borrower or any of its Subsidiaries or any Person acting for Borrower or any of its Subsidiaries makes any representation, warranty, or other statement now or later in this Agreement, any Loan Document or in any writing delivered to Collateral Agent and/or Lenders or to induce Collateral Agent and/or the Lenders to enter this Agreement or any Loan Document, and such representation, warranty, or other statement is incorrect in any material respect when made;

8.9 Subordinated Debt. A default or breach occurs under any agreement between Borrower or any of its Subsidiaries and any creditor of Borrower or any of its Subsidiaries that signed a subordination, intercreditor, or other similar agreement with Collateral Agent or the Lenders, or any creditor that has signed such an agreement with Collateral Agent or the Lenders breaches any terms of such agreement;

8.10 Guaranty. (a) Any Guaranty terminates or ceases for any reason to be in full force and effect; (b) any Guarantor does not perform any obligation or covenant under any Guaranty; (c) any circumstance described in Sections 8.3, 8.4, 8.5, 8.7, or 8.8 occurs with respect to any Guarantor, or (d) the liquidation, winding up, or termination of existence of any Guarantor;

8.11 Governmental Approvals. Any Governmental Approval shall have been revoked, rescinded, suspended, modified in an adverse manner, or not renewed in the ordinary course for a full term *and* such revocation, rescission, suspension, modification or non-renewal has resulted in or could reasonably be expected to result in a Material Adverse Change; or

8.12 Lien Priority. Any Lien created hereunder or by any other Loan Document shall at any time fail to constitute a valid and perfected Lien on any of the Collateral purported to be secured thereby, subject to no prior or equal Lien, other than Permitted Liens which are permitted to have priority in accordance with the terms of this Agreement; provided that such circumstance is not due to Collateral Agent's failure to file an appropriate continuation financing statement, amendment financing statement or initial financing statement.

8.13 Delisting. The shares of common stock of Borrower are delisted from NASDAQ Capital Market because of failure to comply with continued listing standards thereof or due to a voluntary delisting which results in such shares not being listed on any other nationally recognized stock exchange in the United States having listing standards at least as restrictive as the NASDAQ Capital Market.

9. RIGHTS AND REMEDIES

9.1 Rights and Remedies.

(a) Upon the occurrence and during the continuance of an Event of Default, Collateral Agent may, and at the written direction of Required Lenders shall, without notice or demand, do any or all of the following:

(i) deliver notice of the Event of Default to Borrower, (ii) by notice to Borrower declare all Obligations immediately due and payable (but if an Event of Default described in Section 8.5 occurs all Obligations shall be immediately due and payable without any action by Collateral Agent or the Lenders) or (iii) by notice to Borrower suspend or terminate the obligations, if any, of the Lenders to advance money or extend credit for Borrower's benefit under this Agreement or under any other agreement between Borrower and Collateral Agent and/or the Lenders (but if an Event of Default described in Section 8.5 occurs all obligations, if any, of the Lenders to advance money or extend credit for Borrower's benefit under this Agreement or under any other agreement between Borrower and Collateral Agent and/or the Lenders shall be immediately terminated without any action by Collateral Agent or the Lenders).

(b) Without limiting the rights of Collateral Agent and the Lenders set forth in Section 9.1(a) above, upon the occurrence and during the continuance of an Event of Default, Collateral Agent shall have the right, without notice or demand, to do any or all of the following:

(i) foreclose upon and/or sell or otherwise liquidate, the Collateral;

(ii) apply to the Obligations any (a) balances and deposits of Borrower that Collateral Agent or any Lender holds or controls, or (b) any amount held or controlled by Collateral Agent or any Lender owing to or for the credit or the account of Borrower; and/or

(iii) commence and prosecute an Insolvency Proceeding or consent to Borrower commencing any Insolvency Proceeding.

(c) Without limiting the rights of Collateral Agent and the Lenders set forth in Sections 9.1(a) and (b) above, upon the occurrence and during the continuance of an Event of Default, Collateral Agent shall have the right, without notice or demand, to do any or all of the following:

(i) settle or adjust disputes and claims directly with Account Debtors for amounts on terms and in any order that Collateral Agent considers advisable, notify any Person owing Borrower money of Collateral Agent's security interest in such funds, and verify the amount of such account;

(ii) make any payments and do any acts it considers necessary or reasonable to protect the Collateral and/or its security interest in the Collateral. Borrower shall assemble the Collateral if Collateral Agent requests and make it available in a location as Collateral Agent reasonably designates. Collateral Agent may enter premises where the Collateral is located, take and maintain possession of any part of the Collateral, and pay, purchase, contest, or compromise any Lien which appears to be prior or superior to its security interest and pay all expenses incurred. Borrower grants Collateral Agent a license to enter and occupy any of its premises, without charge, to exercise any of Collateral Agent's rights or remedies;

(iii) ship, reclaim, recover, store, finish, maintain, repair, prepare for sale, and/or advertise for sale, the Collateral. Collateral Agent is hereby granted a non-exclusive, royalty-free license or other right to use, without charge, Borrower's and each of its Subsidiaries' labels, patents, copyrights, mask works, rights of use of any name, trade secrets, trade names, trademarks, service marks, and advertising matter, or any similar property as it pertains to the Collateral, in completing production of, advertising for sale, and selling any Collateral and, in connection with Collateral Agent's exercise of its rights under this Section 9.1, Borrower's and each of its Subsidiaries' rights under all licenses and all franchise agreements inure to Collateral Agent, for the benefit of the Lenders;

(iv) place a "hold" on any account maintained with Collateral Agent or the Lenders and/or deliver a notice of exclusive control, any entitlement order, or other directions or instructions pursuant to any Control Agreement or similar agreements providing control of any Collateral;

(v) demand and receive possession of Borrower's Books;

(vi) appoint a receiver to seize, manage and realize any of the Collateral, and such receiver shall have any right and authority as any competent court will grant or authorize in accordance with any applicable law, including any power or authority to manage the business of Borrower or any of its Subsidiaries; and

(vii) subject to clauses 9.1(a) and (b), exercise all rights and remedies available to Collateral Agent and each Lender under the Loan Documents or at law or equity, including all remedies provided under the Code (including disposal of the Collateral pursuant to the terms thereof).

Notwithstanding any provision of this Section 9.1 to the contrary, upon the occurrence of any Event of Default, Collateral Agent shall have the right to exercise any and all remedies referenced in this Section 9.1 without the written consent of Required Lenders following the occurrence of an Exigent Circumstance. As used in the immediately preceding sentence, “**Exigent Circumstance**” means any event or circumstance that, in the reasonable judgment of Collateral Agent, imminently threatens the ability of Collateral Agent to realize upon all or any material portion of the Collateral, such as, without limitation, fraudulent removal, concealment, or abscondment thereof, destruction or material waste thereof, or failure of Borrower or any of its Subsidiaries after reasonable demand to maintain or reinstate adequate casualty insurance coverage, or which, in the judgment of Collateral Agent, could reasonably be expected to result in a material diminution in value of the Collateral.

9.2 Power of Attorney. Borrower hereby irrevocably appoints Collateral Agent as its lawful attorney-in-fact, exercisable upon the occurrence and during the continuance of an Event of Default, to: (a) endorse Borrower’s or any of its Subsidiaries’ name on any checks or other forms of payment or security; (b) sign Borrower’s or any of its Subsidiaries’ name on any invoice or bill of lading for any Account or drafts against Account Debtors; (c) settle and adjust disputes and claims about the Accounts directly with Account Debtors, for amounts and on terms Collateral Agent determines reasonable; (d) make, settle, and adjust all claims under Borrower’s insurance policies; (e) pay, contest or settle any Lien, charge, encumbrance, security interest, and adverse claim in or to the Collateral, or any judgment based thereon, or otherwise take any action to terminate or discharge the same; and (f) transfer the Collateral into the name of Collateral Agent or a third party as the Code or any applicable law permits. Borrower hereby appoints Collateral Agent as its lawful attorney-in-fact to sign Borrower’s or any of its Subsidiaries’ name on any documents necessary to perfect or continue the perfection of Collateral Agent’s security interest in the Collateral regardless of whether an Event of Default has occurred until all Obligations (other than inchoate indemnity obligations) have been satisfied in full and Collateral Agent and the Lenders are under no further obligation to make Credit Extensions hereunder. Collateral Agent’s foregoing appointment as Borrower’s or any of its Subsidiaries’ attorney in fact, and all of Collateral Agent’s rights and powers, coupled with an interest, are irrevocable until all Obligations (other than inchoate indemnity obligations) have been fully repaid and performed and Collateral Agent’s and the Lenders’ obligation to provide Credit Extensions terminates.

9.3 Protective Payments. If Borrower or any of its Subsidiaries fail to obtain the insurance called for by Section 6.5 or fails to pay any premium thereon or fails to pay any other amount which Borrower or any of its Subsidiaries is obligated to pay under this Agreement or any other Loan Document, Collateral Agent may obtain such insurance or make such payment, and all amounts so paid by Collateral Agent are Lenders’ Expenses and immediately due and payable, bearing interest at the Default Rate, and secured by the Collateral. Collateral Agent will make reasonable efforts to provide Borrower with notice of Collateral Agent obtaining such insurance or making such payment at the time it is obtained or paid or within a reasonable time thereafter. No such payments by Collateral Agent are deemed an agreement to make similar payments in the future or Collateral Agent’s waiver of any Event of Default.

9.4 Application of Payments and Proceeds. Notwithstanding anything to the contrary contained in this Agreement, upon the occurrence and during the continuance of an Event of Default, (a) Borrower irrevocably waives the right to direct the application of any and all payments at any time or times thereafter received by Collateral Agent from or on behalf of Borrower or any of its Subsidiaries of all or any part of the Obligations, and, as between Borrower on the one hand and Collateral Agent and Lenders on the other, Collateral Agent shall have the continuing and exclusive right to apply and to reapply any and all payments received against the Obligations in such manner as Collateral Agent may deem advisable notwithstanding any previous application by Collateral Agent, and (b) the proceeds of any sale of, or other realization upon all or any part of the Collateral shall be applied: first, to the Lenders’ Expenses; second, to accrued and unpaid interest on the Obligations (including any interest which, but for the provisions of the United States Bankruptcy Code, would have accrued on such amounts); third, to the principal amount of the Obligations outstanding; and fourth, to any other indebtedness or obligations of Borrower owing to Collateral Agent or any Lender under the Loan Documents. Any balance remaining shall be delivered to Borrower

or to whoever may be lawfully entitled to receive such balance or as a court of competent jurisdiction may direct. In carrying out the foregoing, (x) amounts received shall be applied in the numerical order provided until exhausted prior to the application to the next succeeding category, and (y) each of the Persons entitled to receive a payment in any particular category shall receive an amount equal to its pro rata share of amounts available to be applied pursuant thereto for such category. Any reference in this Agreement to an allocation between or sharing by the Lenders of any right, interest or obligation "ratably," "proportionally" or in similar terms shall refer to Pro Rata Share unless expressly provided otherwise. Collateral Agent, or if applicable, each Lender, shall promptly remit to the other Lenders such sums as may be necessary to ensure the ratable repayment of each Lender's portion of any Term Loan and the ratable distribution of interest, fees and reimbursements paid or made by Borrower. Notwithstanding the foregoing, a Lender receiving a scheduled payment shall not be responsible for determining whether the other Lenders also received their scheduled payment on such date; provided, however, if it is later determined that a Lender received more than its ratable share of scheduled payments made on any date or dates, then such Lender shall remit to Collateral Agent or other Lenders such sums as may be necessary to ensure the ratable payment of such scheduled payments, as instructed by Collateral Agent. If any payment or distribution of any kind or character, whether in cash, properties or securities, shall be received by a Lender in excess of its ratable share, then the portion of such payment or distribution in excess of such Lender's ratable share shall be received by such Lender in trust for and shall be promptly paid over to the other Lender for application to the payments of amounts due on the other Lenders' claims. To the extent any payment for the account of Borrower is required to be returned as a voidable transfer or otherwise, the Lenders shall contribute to one another as is necessary to ensure that such return of payment is on a pro rata basis. If any Lender shall obtain possession of any Collateral, it shall hold such Collateral for itself and as agent and bailee for Collateral Agent and other Lenders for purposes of perfecting Collateral Agent's security interest therein.

9.5 Liability for Collateral. So long as Collateral Agent and the Lenders comply with reasonable banking practices regarding the safekeeping of the Collateral in the possession or under the control of Collateral Agent and the Lenders, Collateral Agent and the Lenders shall not be liable or responsible for: (a) the safekeeping of the Collateral; (b) any loss or damage to the Collateral; (c) any diminution in the value of the Collateral; or (d) any act or default of any carrier, warehouseman, bailee, or other Person. Borrower bears all risk of loss, damage or destruction of the Collateral.

9.6 No Waiver; Remedies Cumulative. Failure by Collateral Agent or any Lender, at any time or times, to require strict performance by Borrower of any provision of this Agreement or any other Loan Document shall not waive, affect, or diminish any right of Collateral Agent or any Lender thereafter to demand strict performance and compliance herewith or therewith. No waiver hereunder shall be effective unless signed by Collateral Agent and the Required Lenders and then is only effective for the specific instance and purpose for which it is given. The rights and remedies of Collateral Agent and the Lenders under this Agreement and the other Loan Documents are cumulative. Collateral Agent and the Lenders have all rights and remedies provided under the Code, any applicable law, by law, or in equity. The exercise by Collateral Agent or any Lender of one right or remedy is not an election, and Collateral Agent's or any Lender's waiver of any Event of Default is not a continuing waiver. Collateral Agent's or any Lender's delay in exercising any remedy is not a waiver, election, or acquiescence.

9.7 Demand Waiver. Borrower waives, to the fullest extent permitted by law, demand, notice of default or dishonor, notice of payment and nonpayment, notice of any default, nonpayment at maturity, release, compromise, settlement, extension, or renewal of accounts, documents, instruments, chattel paper, and guarantees held by Collateral Agent or any Lender on which Borrower or any Subsidiary is liable.

10. NOTICES

All notices, consents, requests, approvals, demands, or other communication (collectively, "**Communication**") by any party to this Agreement or any other Loan Document must be in writing and shall be deemed to have been validly served, given, or delivered: (a) upon the earlier of actual receipt and three (3) Business Days after deposit in the U.S. mail, first class, registered or certified mail return receipt requested, with proper postage prepaid; (b) upon transmission, when sent by facsimile transmission or email (if an email is specified herein); (c) one (1) Business Day after deposit with a reputable overnight courier with all charges prepaid; or (d) when delivered, if hand-delivered by messenger, all of which shall be addressed to the party to be notified and sent to the address, facsimile number, or email address indicated below. Any of Collateral Agent, Lender or Borrower may change its mailing address, email address or facsimile number by giving the other party written notice thereof in accordance with the terms of this Section 10.

If to Borrower: SYROS PHARMACEUTICALS, INC.
35 CambridgePark Drive
Cambridge, MA 02140
Attn: Chief Financial Officer and Chief Legal Officer

with a copy (which shall not constitute notice) to: Wilmer Cutler Pickering Hale and Dorr, LLP
1225 Seventeenth St., Suite 2600
Denver, CO 80202 USA
Attn: Chalyse Robinson
Fax: (720) 274-3133
Email: chalyse.robinson@wilmerhale.com

If to Collateral Agent: OXFORD FINANCE LLC
133 North Fairfax Street
Alexandria, Virginia 22314
Attention: Legal Department
Fax: (703) 519-5225
Email: LegalDepartment@oxfordfinance.com

with a copy (which shall not constitute notice) to: DLA Piper LLP (US)
500 8th Street, NW
Washington, DC 20004
Attn: Eric Eisenberg
Fax: (202) 799-5211
Email: eric.eisenberg@dlapiper.com

11. CHOICE OF LAW, VENUE AND JURY TRIAL WAIVER, AND JUDICIAL REFERENCE

New York law governs the Loan Documents without regard to principles of conflicts of law. Borrower, Collateral Agent and each Lender each submit to the exclusive jurisdiction of the State and Federal courts in the city of New York, New York, Borough of Manhattan; provided, however, that nothing in this Agreement shall be deemed to operate to preclude Collateral Agent or any Lender from bringing suit or taking other legal action in any other jurisdiction to realize on the Collateral or any other security for the Obligations, or to enforce a judgment or other court order in favor of Collateral Agent or any Lender. Borrower expressly submits and consents in advance to such jurisdiction in any action or suit commenced in any such court, and Borrower hereby waives any objection that it may have based upon lack of personal jurisdiction, improper venue, or forum non conveniens and hereby consents to the granting of such legal or equitable relief as is deemed appropriate by such court. Borrower hereby waives personal service of the summons, complaints, and other process issued in such action or suit and agrees that service of such summons, complaints, and other process may be made by registered or certified mail addressed to Borrower at the address set forth in, or subsequently provided by Borrower in accordance with, Section 10 of this Agreement and that service so made shall be deemed completed upon the earlier to occur of Borrower's actual receipt thereof or three (3) days after deposit in the U.S. mail, first class, registered or certified mail return receipt requested, proper postage prepaid.

TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, BORROWER, COLLATERAL AGENT AND EACH LENDER EACH WAIVE THEIR RIGHT TO A JURY TRIAL OF ANY CLAIM OR CAUSE OF ACTION ARISING OUT OF OR BASED UPON THIS AGREEMENT, THE LOAN DOCUMENTS OR ANY CONTEMPLATED TRANSACTION, INCLUDING CONTRACT, TORT, BREACH OF DUTY AND ALL OTHER CLAIMS. THIS WAIVER IS A MATERIAL INDUCEMENT FOR EACH PARTY TO ENTER INTO THIS AGREEMENT. EACH PARTY HAS REVIEWED THIS WAIVER WITH ITS COUNSEL.

12. GENERAL PROVISIONS

12.1 Successors and Assigns. This Agreement binds and is for the benefit of the successors and permitted assigns of each party. Borrower may not transfer, pledge or assign this Agreement or any rights or obligations under it without Collateral Agent's and each Lender's prior written consent (which may be granted or withheld in

Collateral Agent's and each Lender's discretion, subject to Section 12.6). The Lenders have the right, without the consent of or notice to Borrower, to sell, transfer, assign, pledge, negotiate, or grant participation in **(any** such sale, transfer, assignment, negotiation, or grant of a participation, a **"Lender Transfer"**) all or any part of, or any interest in, the Lenders' obligations, rights, and benefits under this Agreement and the other Loan Documents; *provided, however*, that any such Lender Transfer (other than a transfer, pledge, sale or assignment to an Eligible Assignee) of its obligations, rights, and benefits under this Agreement and the other Loan Documents shall require the prior written consent of the Required Lenders (such approved assignee, an **"Approved Lender"**). Borrower and Collateral Agent shall be entitled to continue to deal solely and directly with such Lender in connection with the interests so assigned until Collateral Agent shall have received and accepted an effective assignment agreement in form satisfactory to Collateral Agent executed, delivered and fully completed by the applicable parties thereto, and shall have received such other information regarding such Eligible Assignee or Approved Lender as Collateral Agent reasonably shall require. Notwithstanding anything to the contrary contained herein, so long as no Event of Default has occurred and is continuing, no Lender Transfer (other than a Lender Transfer (i) in respect of the Warrants or (ii) in connection with (x) assignments by a Lender due to a forced divestiture at the request of any regulatory agency; or (y) upon the occurrence of a default, event of default or similar occurrence with respect to a Lender's own financing or securitization transactions) shall be permitted, without Borrower's consent, to any Person which is an Affiliate or Subsidiary of Borrower, a direct competitor of Borrower or a vulture hedge fund, each as determined by Collateral Agent.

12.2 Indemnification. Borrower agrees to indemnify, defend and hold Collateral Agent and the Lenders and their respective directors, officers, employees, agents, attorneys, or any other Person affiliated with or representing Collateral Agent or the Lenders (each, an **"Indemnified Person"**) harmless against: (a) all obligations, demands, claims, and liabilities (collectively, **"Claims"**) asserted by any other party in connection with; related to; following; or arising from, out of or under, the transactions contemplated by the Loan Documents; and (b) all losses or Lenders' Expenses incurred, or paid by Indemnified Person in connection with; related to; following; or arising from, out of or under, the transactions contemplated by the Loan Documents between Collateral Agent, and/or the Lenders and Borrower (including reasonable and documented attorneys' fees and expenses), except for Claims and/or losses directly caused by such Indemnified Person's gross negligence or willful misconduct. Borrower hereby further indemnifies, defends and holds each Indemnified Person harmless from and against any and all liabilities, obligations, losses, damages, penalties, actions, judgments, suits, claims, costs, expenses and disbursements of any kind or nature whatsoever (including the reasonable and documented fees and disbursements of counsel for such Indemnified Person) in connection with any investigative, response, remedial, administrative or judicial matter or proceeding, whether or not such Indemnified Person shall be designated a party thereto and including any such proceeding initiated by or on behalf of Borrower, and the reasonable expenses of investigation by engineers, environmental consultants and similar technical personnel and any commission, fee or compensation claimed by any broker (other than any broker retained by Collateral Agent or Lenders) asserting any right to payment for the transactions contemplated hereby which may be imposed on, incurred by or asserted against such Indemnified Person as a result of or in connection with the transactions contemplated hereby and the use or intended use of the proceeds of the loan proceeds except for liabilities, obligations, losses, damages, penalties, actions, judgments, suits, claims, costs, expenses and disbursements directly caused by such Indemnified Person's gross negligence or willful misconduct.

12.3 Time of Essence. Time is of the essence for the performance of all Obligations in this Agreement.

12.4 Severability of Provisions. Each provision of this Agreement is severable from every other provision in determining the enforceability of any provision.

12.5 Correction of Loan Documents. Collateral Agent and the Lenders may correct patent errors and fill in any blanks in this Agreement and the other Loan Documents consistent with the agreement of the parties so long as Collateral Agent provides Borrower with written notice of such correction and allows Borrower at least ten (10) days to object to such correction. In the event of such objection, such correction shall not be made except by an amendment signed by both Collateral Agent and Borrower.

12.6 Amendments in Writing; Integration. (a) No amendment, modification, termination or waiver of any provision of this Agreement or any other Loan Document, no approval or consent thereunder, or any consent to any departure by Borrower or any of its Subsidiaries therefrom, shall in any event be effective unless the same shall be in writing and signed by Borrower, Collateral Agent and the Required Lenders provided that:

(i) no such amendment, waiver or other modification that would have the effect of increasing or reducing a Lender's Term Loan Commitment or Commitment Percentage shall be effective as to such Lender without such Lender's written consent;

(ii) no such amendment, waiver or modification that would affect the rights and duties of Collateral Agent shall be effective without Collateral Agent's written consent or signature;

(iii) no such amendment, waiver or other modification shall, unless signed by all the Lenders directly affected thereby, (A) reduce the principal of, rate of interest on or any fees with respect to any Term Loan or forgive any principal, interest (other than default interest) or fees (other than late charges) with respect to any Term Loan (B) postpone the date fixed for, or waive, any payment of principal of any Term Loan or of interest on any Term Loan (other than default interest) or any fees provided for hereunder (other than late charges or for any termination of any commitment); (C) change the definition of the term "**Required Lenders**" or the percentage of Lenders which shall be required for the Lenders to take any action hereunder; (D) release all or substantially all or any material portion of the Collateral, authorize Borrower to sell or otherwise dispose of all or substantially all or any material portion of the Collateral or release any Guarantor of all or any portion of the Obligations or its guaranty obligations with respect thereto, except, in each case with respect to this clause (D), as otherwise may be expressly permitted under this Agreement or the other Loan Documents (including in connection with any disposition permitted hereunder); (E) amend, waive or otherwise modify this Section 12.6 or the definitions of the terms used in this Section 12.6 insofar as the definitions affect the substance of this Section 12.6; (F) consent to the assignment, delegation or other transfer by Borrower of any of its rights and obligations under any Loan Document or release Borrower of its payment obligations under any Loan Document, except, in each case with respect to this clause (F), pursuant to a merger or consolidation permitted pursuant to this Agreement; (G) amend any of the provisions of Section 9.4 or amend any of the definitions of Pro Rata Share, Term Loan Commitment, Commitment Percentage or that provide for the Lenders to receive their Pro Rata Shares of any fees, payments, setoffs or proceeds of Collateral hereunder; (H) subordinate the Liens granted in favor of Collateral Agent securing the Obligations; or (I) amend any of the provisions of Section 12.10. It is hereby understood and agreed that all Lenders shall be deemed directly affected by an amendment, waiver or other modification of the type described in the preceding clauses (C), (D), (E), (F), (G) and (H) of the preceding sentence;

(iv) the provisions of the foregoing clauses (i), (ii) and (iii) are subject to the provisions of any interlender or agency agreement among the Lenders and Collateral Agent pursuant to which any Lender may agree to give its consent in connection with any amendment, waiver or modification of the Loan Documents only in the event of the unanimous agreement of all Lenders.

(b) Other than as expressly provided for in Section 12.6(a)(i)-(iii), Collateral Agent may, if requested by the Required Lenders, from time to time designate covenants in this Agreement less restrictive by notification to a representative of Borrower.

(c) This Agreement and the Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements. All prior agreements, understandings, representations, warranties, and negotiations between the parties about the subject matter of this Agreement and the Loan Documents merge into this Agreement and the Loan Documents.

12.7 Counterparts. This Agreement may be executed in any number of counterparts and by different parties on separate counterparts, each of which, when executed and delivered, is an original, and all taken together, constitute one Agreement.

12.8 Survival. All covenants, representations and warranties made in this Agreement continue in full force and effect until this Agreement has terminated pursuant to its terms and all Obligations (other than inchoate indemnity obligations and any other obligations which, by their terms, are to survive the termination of this Agreement) have been satisfied. The obligation of Borrower in Section 12.2 to indemnify each Lender and Collateral Agent, as well as the confidentiality provisions in Section 12.9 below, shall survive until the statute of limitations with respect to such claim or cause of action shall have run.

12.9 Confidentiality. In handling any confidential information of Borrower and its Subsidiaries, the Lenders and Collateral Agent shall exercise the same degree of care that it exercises for their own proprietary

information, but disclosure of information may be made: (a) subject to the terms and conditions of this Agreement, to the Lenders' and Collateral Agent's Subsidiaries or Affiliates, or in connection with a Lender's own financing or securitization transactions and upon the occurrence of a default, event of default or similar occurrence with respect to such financing or securitization transaction; (b) to prospective transferees (other than those identified in (a) above) or purchasers of any interest in the Credit Extensions (provided, however, the Lenders and Collateral Agent shall, except upon the occurrence and during the continuance of an Event of Default, obtain such prospective transferee's or purchaser's agreement to the terms of this provision or to similar confidentiality terms); (c) as required by law, regulation, subpoena, or other order; (d) to Lenders' or Collateral Agent's regulators or as otherwise required in connection with an examination or audit; (e) as Collateral Agent reasonably considers appropriate in exercising remedies under the Loan Documents; and (f) to third party service providers of the Lenders and/or Collateral Agent so long as such service providers have executed a confidentiality agreement with the Lenders and Collateral Agent with terms no less restrictive than those contained herein. Confidential information does not include information that either: (i) is in the public domain or in the Lenders' and/or Collateral Agent's possession when disclosed to the Lenders and/or Collateral Agent, or becomes part of the public domain after disclosure to the Lenders and/or Collateral Agent; or (ii) is disclosed to the Lenders and/or Collateral Agent by a third party, if the Lenders and/or Collateral Agent does not know that the third party is prohibited from disclosing the information. Collateral Agent and the Lenders may use confidential information for any purpose relating to the administration of this Agreement, including, without limitation, for the development of client databases, reporting purposes, and market analysis, in each case without any identifying information regarding the Borrower or its Subsidiaries. The provisions of the immediately preceding sentence shall survive the termination of this Agreement. The agreements provided under this Section 12.9 supersede all prior agreements, understanding, representations, warranties, and negotiations between the parties about the subject matter of this Section 12.9.

12.10 Right of Set Off. Borrower hereby grants to Collateral Agent and to each Lender, a lien, security interest and right of set off as security for all Obligations to Collateral Agent and each Lender hereunder, whether now existing or hereafter arising upon and against all deposits, credits, collateral and property, now or hereafter in the possession, custody, safekeeping or control of Collateral Agent or the Lenders or any entity under the control of Collateral Agent or the Lenders (including a Collateral Agent affiliate) or in transit to any of them. At any time after the occurrence and during the continuance of an Event of Default, without demand or notice, Collateral Agent or the Lenders may set off the same or any part thereof and apply the same to any liability or obligation of Borrower even though unmatured and regardless of the adequacy of any other collateral securing the Obligations. ANY AND ALL RIGHTS TO REQUIRE COLLATERAL AGENT TO EXERCISE ITS RIGHTS OR REMEDIES WITH RESPECT TO ANY OTHER COLLATERAL WHICH SECURES THE OBLIGATIONS, PRIOR TO EXERCISING ITS RIGHT OF SETOFF WITH RESPECT TO SUCH DEPOSITS, CREDITS OR OTHER PROPERTY OF BORROWER ARE HEREBY KNOWINGLY, VOLUNTARILY AND IRREVOCABLY WAIVED.

12.11 Cooperation of Borrower. If necessary, Borrower agrees to (i) execute any documents (including new Secured Promissory Notes) reasonably required to effectuate and acknowledge each assignment of a Term Loan Commitment or Loan to an assignee in accordance with Section 12.1, (ii) make Borrower's management available to meet with Collateral Agent and prospective participants and assignees of Term Loan Commitments or Credit Extensions (which meetings shall be conducted during normal business hours and upon reasonable prior written notice no more often than twice every twelve months unless an Event of Default has occurred and is continuing), and (iii) assist Collateral Agent or the Lenders in the preparation of information relating to the financial affairs of Borrower as any prospective participant or assignee of a Term Loan Commitment or Term Loan reasonably may request. Subject to the provisions of Section 12.9, Borrower authorizes each Lender to disclose to any prospective participant or assignee of a Term Loan Commitment, any and all information in such Lender's possession concerning Borrower and its financial affairs which has been delivered to such Lender by or on behalf of Borrower pursuant to this Agreement, or which has been delivered to such Lender by or on behalf of Borrower in connection with such Lender's credit evaluation of Borrower prior to entering into this Agreement.

13. DEFINITIONS

13.1 Definitions. As used in this Agreement, the following terms have the following meanings:

"**Account**" is any "account" as defined in the Code with such additions to such term as may hereafter be made, and includes, without limitation, all accounts receivable and other sums owing to Borrower.

“**Account Debtor**” is any “account debtor” as defined in the Code with such additions to such term as may hereafter be made.

“**Affiliate**” of any Person is a Person that owns or controls directly or indirectly the Person, any Person that controls or is controlled by or is under common control with the Person, and each of that Person’s senior executive officers, directors, partners and, for any Person that is a limited liability company, that Person’s managers and members.

“**Agreement**” is defined in the preamble hereof.

“**Amortization Date**” is March 1, 2023.

“**Annual Projections**” is defined in Section 6.2(a).

“**Anti-Terrorism Laws**” are any laws relating to terrorism or money laundering, including Executive Order No. 13224 (effective September 24, 2001), the USA PATRIOT Act, the laws comprising or implementing the Bank Secrecy Act, and the laws administered by OFAC.

“**Approved Fund**” is any (i) investment company, fund, trust, securitization vehicle or conduit that is (or will be) engaged in making, purchasing, holding or otherwise investing in commercial loans and similar extensions of credit in the ordinary course of its business or (ii) any Person (other than a natural person) which temporarily warehouses loans for any Lender or any entity described in the preceding clause (i) and that, with respect to each of the preceding clauses (i) and (ii), is administered or managed by (a) a Lender, (b) an Affiliate of a Lender or (c) a Person (other than a natural person) or an Affiliate of a Person (other than a natural person) that administers or manages a Lender.

“**Approved Lender**” is defined in Section 12.1.

“**Basic Rate**” is the per annum rate of interest (based on a year of three hundred sixty (360) days) equal to the greater of (i) seven and three-fourths of one percent (7.75%) and (ii) the sum of five and ninety-eight hundredths of one percent (5.98%) and the greater of (A) the thirty (30) day U.S. LIBOR rate (the “**Index Rate**”) reported in The Wall Street Journal on the last Business Day of the month that immediately precedes the month in which the interest will accrue and (B) one and seventy-seven hundredths of one percent (1.77%). If The Wall Street Journal (or another nationally recognized rate reporting source acceptable to Collateral Agent) no longer reports the U.S. LIBOR Rate or if such interest rate no longer exists or if The Wall Street Journal no longer publishes the U.S. LIBOR Rate or ceases to exist, Collateral Agent may in good faith, and with reference to the margin above such interest rate in this definition, select a replacement interest rate and replacement margin above such interest rate or replacement publication, as the case may be, that results in a substantially similar interest rate floor and total rate in effect immediately prior to the effectiveness of such replacement interest rate and replacement margin, or replacement publication, as the case may be, and shall notify Borrower of such replacement interest rate and replacement margin or replacement publication. Notwithstanding the foregoing, the Basic Rate for the Term Loans for the period from the Effective Date through and including February 29, 2020 shall be seven and three-fourths of one percent (7.75%).

“**Blocked Person**” is any Person: (a) listed in the annex to, or is otherwise subject to the provisions of, Executive Order No. 13224, (b) a Person owned or controlled by, or acting for or on behalf of, any Person that is listed in the annex to, or is otherwise subject to the provisions of, Executive Order No. 13224, (c) a Person with which any Lender is prohibited from dealing or otherwise engaging in any transaction by any Anti-Terrorism Law, (d) a Person that commits, threatens or conspires to commit or supports “terrorism” as defined in Executive Order No. 13224, or (e) a Person that is named a “specially designated national” or “blocked person” on the most current list published by OFAC or other similar list.

“**Borrower**” is defined in the preamble hereof.

“**Borrower’s Books**” are Borrower’s or any of its Subsidiaries’ books and records including ledgers, federal, and state tax returns, records regarding Borrower’s or its Subsidiaries’ assets or liabilities, the Collateral, business operations or financial condition, and all computer programs or storage or any equipment containing such information.

“**Business Day**” is any day that is not a Saturday, Sunday or a day on which Collateral Agent is closed.

“**Cash Equivalents**” are (a) marketable direct obligations issued or unconditionally guaranteed by the United States or any agency or any State thereof having maturities of not more than one (1) year from the date of acquisition; (b) commercial paper maturing no more than one (1) year after its creation and having the highest rating from either Standard & Poor’s Ratings Group or Moody’s Investors Service, Inc., (c) certificates of deposit maturing no more than one (1) year after issue provided that the account in which any such certificate of deposit is maintained is subject to a Control Agreement in favor of Collateral Agent and (d) money market funds at least ninety-five percent (95.00%) of the assets of which constitute Cash Equivalents of the kinds described in clauses (a) through (c) of this definition. For the avoidance of doubt, the direct purchase by Borrower or any of its Subsidiaries of any Auction Rate Securities, or purchasing participations in, or entering into any type of swap or other derivative transaction, or otherwise holding or engaging in any ownership interest in any type of Auction Rate Security by Borrower or any of its Subsidiaries shall be conclusively determined by the Lenders as an ineligible Cash Equivalent, and any such transaction shall expressly violate each other provision of this Agreement governing Permitted Investments. Notwithstanding the foregoing, Cash Equivalents does not include and Borrower, and each of its Subsidiaries, are prohibited from purchasing, purchasing participations in, entering into any type of swap or other equivalent derivative transaction, or otherwise holding or engaging in any ownership interest in any type of debt instrument, including, without limitation, any corporate or municipal bonds with a long-term nominal maturity for which the interest rate is reset through a dutch auction and more commonly referred to as an auction rate security (each, an “**Auction Rate Security**”).

“**Claims**” are defined in Section 12.2.

“**Code**” is the Uniform Commercial Code, as the same may, from time to time, be enacted and in effect in the State of New York; provided, that, to the extent that the Code is used to define any term herein or in any Loan Document and such term is defined differently in different Articles of the Code, the definition of such term contained in Article 9 shall govern; provided further, that in the event that, by reason of mandatory provisions of law, any or all of the attachment, perfection, or priority of, or remedies with respect to, Collateral Agent’s Lien on any Collateral is governed by the Uniform Commercial Code in effect in a jurisdiction other than the State of New York, the term “Code” shall mean the Uniform Commercial Code as enacted and in effect in such other jurisdiction solely for purposes of the provisions thereof relating to such attachment, perfection, priority, or remedies and for purposes of definitions relating to such provisions.

“**Collateral**” is any and all properties, rights and assets of Borrower described on Exhibit A.

“**Collateral Account**” is any Deposit Account, Securities Account, or Commodity Account, or any other bank account maintained by Borrower or any Guarantor at any time.

“**Collateral Agent**” is, Oxford, not in its individual capacity, but solely in its capacity as agent on behalf of and for the benefit of the Lenders.

“**Commitment Percentage**” is set forth in Schedule 1.1, as amended from time to time.

“**Commodity Account**” is any “commodity account” as defined in the Code with such additions to such term as may hereafter be made.

“**Communication**” is defined in Section 10.

“**Compliance Certificate**” is that certain certificate in the form attached hereto as Exhibit C.

“**Contingent Obligation**” is, for any Person, any direct or indirect liability, contingent or not, of that Person for (a) any indebtedness, lease, dividend, letter of credit or other obligation of another such as an obligation directly or indirectly guaranteed, endorsed, co-made, discounted or sold with recourse by that Person, or for which that Person is directly or indirectly liable; (b) any obligations for undrawn letters of credit for the account of that Person; and (c) all obligations from any interest rate, currency or commodity swap agreement, interest rate cap or collar agreement, or other agreement or arrangement designated to protect a Person against fluctuation in interest rates, currency exchange rates or commodity prices; but “Contingent Obligation” does not include endorsements in the

ordinary course of business. The amount of a Contingent Obligation is the stated or determined amount of the primary obligation for which the Contingent Obligation is made or, if not determinable, the maximum reasonably anticipated liability for it determined by the Person in good faith; but the amount may not exceed the maximum of the obligations under any guarantee or other support arrangement.

“**Control Agreement**” is any control agreement entered into among the depository institution at which any Loan Party maintains a Deposit Account or the securities intermediary or commodity intermediary at which any Loan Party maintains a Securities Account or a Commodity Account, such Loan Party, and Collateral Agent pursuant to which Collateral Agent obtains control (within the meaning of the Code) for the benefit of the Lenders over such Deposit Account, Securities Account, or Commodity Account.

“**Copyrights**” are any and all copyright rights, copyright applications, copyright registrations and like protections in each work or authorship and derivative work thereof, whether published or unpublished and whether or not the same also constitutes a trade secret.

“**Credit Extension**” is any Term Loan or any other extension of credit by Collateral Agent or Lenders for Borrower’s benefit.

“**Default Rate**” is defined in Section 2.3(b).

“**Deposit Account**” is any “deposit account” as defined in the Code with such additions to such term as may hereafter be made.

“**Designated Deposit Account**” is Borrower’s deposit account maintained with Silicon Valley Bank and identified on the Perfection Certificate as its Designated Deposit Account.

“**Disbursement Letter**” is that certain form attached hereto as Exhibit B.

“**Dollars**,” “**dollars**” and “**\$**” each mean lawful money of the United States.

“**Domestic Subsidiary**” means a Subsidiary organized under the laws of the United States or any state or territory thereof or the District of Columbia.

“**Effective Date**” is defined in the preamble of this Agreement.

“**Eligible Assignee**” is (i) a Lender, (ii) an Affiliate of a Lender, (iii) an Approved Fund and (iv) any commercial bank, savings and loan association or savings bank or any other entity which is an “accredited investor” (as defined in Regulation D under the Securities Act of 1933, as amended) and which extends credit or buys loans as one of its businesses, including insurance companies, mutual funds, lease financing companies and commercial finance companies, in each case, which either (A) has a rating of BBB or higher from Standard & Poor’s Rating Group and a rating of Baa2 or higher from Moody’s Investors Service, Inc. at the date that it becomes a Lender or (B) has total assets in excess of Five Billion Dollars (\$5,000,000,000.00), and in each case of clauses (i) through (iv), which, through its applicable lending office, is capable of lending to Borrower without the imposition of any withholding or similar taxes; provided that notwithstanding the foregoing, “Eligible Assignee” shall not include, unless an Event of Default has occurred and is continuing, (i) Borrower or any of Borrower’s Affiliates or Subsidiaries or (ii) a direct competitor of Borrower or a vulture hedge fund, each as determined by Collateral Agent. Notwithstanding the foregoing, (x) in connection with assignments by a Lender due to a forced divestiture at the request of any regulatory agency, the restrictions set forth herein shall not apply and Eligible Assignee shall mean any Person or party and (y) in connection with a Lender’s own financing or securitization transactions, the restrictions set forth herein shall not apply and Eligible Assignee shall mean any Person or party providing such financing or formed to undertake such securitization transaction and any transferee of such Person or party upon the occurrence of a default, event of default or similar occurrence with respect to such financing or securitization transaction; provided that no such sale, transfer, pledge or assignment under this clause (y) shall release such Lender from any of its obligations hereunder or substitute any such Person or party for such Lender as a party hereto until Collateral Agent shall have received and accepted an effective assignment agreement from such Person or party in form satisfactory to Collateral Agent executed, delivered and fully completed by the applicable parties thereto, and

shall have received such other information regarding such Eligible Assignee as Collateral Agent reasonably shall require.

“**Equipment**” is all “equipment” as defined in the Code with such additions to such term as may hereafter be made, and includes without limitation all machinery, fixtures, goods, vehicles (including motor vehicles and trailers), and any interest in any of the foregoing.

“**ERISA**” is the Employee Retirement Income Security Act of 1974, as amended, and its regulations.

“**Event of Default**” is defined in Section 8.

“**Excluded Taxes**” means, with respect to a Lender, any Taxes imposed on or measured by net income (however denominated), franchise Taxes, and branch profits Taxes imposed as a result of such Lender being organized under the laws of, or having its principal office or its applicable lending office located in, the jurisdiction imposing such Tax (or any political subdivision thereof) or that are imposed as a result of a present or former connection between such Lender and the jurisdiction imposing such Tax (other than connections arising solely from such Lender becoming a party to this Agreement and performing its obligations and receiving payments under such Agreement).

“**Facility Fee**” is defined in Section 2.5(a).

“**Final Payment**” is a payment (in addition to and not a substitution for the regular monthly payments of principal plus accrued interest) due on the earliest to occur of (a) the Maturity Date, or (b) the acceleration of any Term Loan, or (c) the prepayment of a Term Loan pursuant to Section 2.2(c) or (d), equal to the original principal amount of such funded Term Loan being repaid, multiplied by the Final Payment Percentage, payable to Lenders in accordance with their respective Pro Rata Shares.

“**Final Payment Percentage**” is five percent (5.00%).

“**Foreign Subsidiary**” means any Subsidiary which is not a Domestic Subsidiary.

“**Funding Date**” is any date on which a Credit Extension is made to or on account of Borrower which shall be a Business Day.

“**GAAP**” is generally accepted accounting principles set forth in the opinions and pronouncements of the Accounting Principles Board of the American Institute of Certified Public Accountants and statements and pronouncements of the Financial Accounting Standards Board or in such other statements by such other Person as may be approved by a significant segment of the accounting profession in the United States, which are applicable to the circumstances as of the date of determination.

“**GBT Agreement**” means that certain License and Collaboration Agreement between Global Blood Therapeutics, Inc. and Borrower dated as of December 17, 2019, as in effect on the Effective Date.

“**General Intangibles**” are all “general intangibles” as defined in the Code in effect on the date hereof with such additions to such term as may hereafter be made, and includes without limitation, all copyright rights, copyright applications, copyright registrations and like protections in each work of authorship and derivative work, whether published or unpublished, any patents, trademarks, service marks and, to the extent permitted under applicable law, any applications therefor, whether registered or not, any trade secret rights, including any rights to unpatented inventions, payment intangibles, royalties, contract rights, goodwill, franchise agreements, purchase orders, customer lists, route lists, telephone numbers, domain names, claims, income and other tax refunds, security and other deposits, options to purchase or sell real or personal property, rights in all litigation presently or hereafter pending (whether in contract, tort or otherwise), insurance policies (including without limitation key man, property damage, and business interruption insurance), payments of insurance and rights to payment of any kind.

“**Governmental Approval**” is any consent, authorization, approval, order, license, franchise, permit, certificate, accreditation, registration, filing or notice, of, issued by, from or to, or other act by or in respect of, any Governmental Authority.

“Governmental Authority” is any nation or government, any state or other political subdivision thereof, any agency, authority, instrumentality, regulatory body, court, central bank or other entity exercising executive, legislative, judicial, taxing, regulatory or administrative functions of or pertaining to government, any securities exchange and any self-regulatory organization.

“Guarantor” is any Person providing a Guaranty in favor of Collateral Agent. As of the Effective Date, there are no Guarantors.

“Guaranty” is any guarantee of all or any part of the Obligations, as the same may from time to time be amended, restated, modified or otherwise supplemented.

“Incyte Agreement” means that certain Target Discovery, Research Collaboration and Option Agreement between Incyte Corporation and Borrower dated as of January 8, 2018, as amended prior to the Effective Date and as in effect on the Effective Date.

“Indebtedness” is (a) indebtedness for borrowed money or the deferred price of property or services, such as reimbursement and other obligations for surety bonds and letters of credit, (b) obligations evidenced by notes, bonds, debentures or similar instruments, (c) capital lease obligations, and (d) Contingent Obligations.

“Indemnified Person” is defined in Section 12.2.

“Insolvency Proceeding” is any proceeding by or against any Person under the United States Bankruptcy Code, or any other bankruptcy or insolvency law, including assignments for the benefit of creditors, compositions, extensions generally with its creditors, or proceedings seeking reorganization, arrangement, or other relief.

“Insolvent” means not Solvent.

“Intellectual Property” means all of Borrower’s or any Subsidiary’s right, title and interest in and to the following:

- (a) its Copyrights, Trademarks and Patents;
- (b) any and all trade secrets and trade secret rights, including, without limitation, any rights to unpatented inventions, know-how, operating manuals;
- (c) any and all source code;
- (d) any and all design rights which may be available to Borrower;
- (e) any and all claims for damages by way of past, present and future infringement of any of the foregoing, with the right, but not the obligation, to sue for and collect such damages for said use or infringement of the Intellectual Property rights identified above; and
- (f) all amendments, renewals and extensions of any of the Copyrights, Trademarks or Patents.

“Inventory” is all “inventory” as defined in the Code in effect on the date hereof with such additions to such term as may hereafter be made, and includes without limitation all merchandise, raw materials, parts, supplies, packing and shipping materials, work in process and finished products, including without limitation such inventory as is temporarily out of any Person’s custody or possession or in transit and including any returned goods and any documents of title representing any of the above.

“Investment” is any beneficial ownership interest in any Person (including stock, partnership interest or other securities), and any loan, advance, capital contribution or similar payment to any Person.

“Key Person” is each of Borrower’s (i) Chief Executive Officer, who is Nancy Simonian as of the Effective Date and (ii) Chief Financial Officer, who is Joseph Ferra as of the Effective Date.

“**Lender**” is any one of the Lenders.

“**Lenders**” are the Persons identified on Schedule 1.1 hereto and each assignee that becomes a party to this Agreement pursuant to Section 12.1.

“**Lenders’ Expenses**” are all reasonable and documented expenses for audit fees and expenses, and costs and expenses (including reasonable attorneys’ fees and expenses, as well as appraisal fees, fees incurred on account of lien searches, inspection fees, and filing fees) for preparing, amending, negotiating, administering, defending and enforcing the Loan Documents (including, without limitation, those incurred in connection with appeals or Insolvency Proceedings) or otherwise incurred by Collateral Agent and/or the Lenders in connection with the Loan Documents.

“**Lien**” is a claim, mortgage, deed of trust, levy, charge, pledge, security interest, or other encumbrance of any kind, whether voluntarily incurred or arising by operation of law or otherwise against any property.

“**Loan Documents**” are, collectively, this Agreement, the Warrants, the Perfection Certificates, each Compliance Certificate, each Disbursement Letter, the Post Closing Letter, the Officer’s Certificate, any subordination agreements, any note, or notes or guaranties executed by Borrower or any other Person, and any other present or future agreement entered into by Borrower, any Guarantor or any other Person for the benefit of the Lenders and Collateral Agent in connection with this Agreement; all as amended, restated, or otherwise modified.

“**Loan Party**” is each of Borrower and any Subsidiary of Borrower that is a co borrower or Guarantor hereunder.

“**Material Adverse Change**” is (a) a material impairment in the perfection or priority of Collateral Agent’s Lien in the Collateral or in the value of such Collateral; (b) a material adverse change in the business, operations or condition (financial or otherwise) of Borrower, or Borrower and its Subsidiaries, taken as a whole; or (c) a material impairment of the prospect of repayment of any portion of the Obligations.

“**Maturity Date**” is February 1, 2025.

“**MSC Investments Condition**” is defined in Section 6.10.

“**Obligations**” are all of Borrower’s obligations to pay when due any debts, principal, interest, Lenders’ Expenses, the Prepayment Fee, the Final Payment, and other amounts Borrower owes the Lenders now or later, in connection with, related to, following, or arising from, out of or under, this Agreement or, the other Loan Documents (other than the Warrants), or otherwise, and including interest accruing after Insolvency Proceedings begin (whether or not allowed) and debts, liabilities, or obligations of Borrower assigned to the Lenders and/or Collateral Agent, and the performance of Borrower’s duties under the Loan Documents (other than the Warrants).

“**OFAC**” is the U.S. Department of Treasury Office of Foreign Assets Control.

“**OFAC Lists**” are, collectively, the Specially Designated Nationals and Blocked Persons List maintained by OFAC pursuant to Executive Order No. 13224, 66 Fed. Reg. 49079 (Sept. 25, 2001) and/or any other list of terrorists or other restricted Persons maintained pursuant to any of the rules and regulations of OFAC or pursuant to any other applicable Executive Orders.

“**Operating Documents**” are, for any Person, such Person’s formation documents, as certified by the Secretary of State (or equivalent agency) of such Person’s jurisdiction of organization on a date that is no earlier than thirty (30) days prior to the Effective Date, and, (a) if such Person is a corporation, its bylaws in current form, (b) if such Person is a limited liability company, its limited liability company agreement (or similar agreement), and (c) if such Person is a partnership, its partnership agreement (or similar agreement), each of the foregoing with all current amendments or modifications thereto.

“**Patents**” means all patents, patent applications and like protections including without limitation improvements, divisions, continuations, renewals, reissues, extensions and continuations-in-part of the same.

“Payment Date” is the first (1st) calendar day of each calendar month, commencing on April 1, 2020.

“Perfection Certificate” and **“Perfection Certificates”** is defined in Section 5.1.

“Permitted Acquisition” means an acquisition pursuant to which Borrower acquires a Person or an ownership interest in a Person, or some or all of the assets of such Person through either (i) the payment of cash consideration of no more than One Million Dollars (\$1,000,000.00) with respect to any one acquisition and in the aggregate per fiscal year, or (ii) the issuance of Borrower’s capital stock, so long as the number of shares or the voting power of Borrower’s capital stock issued with respect to any one Person is less than ten percent (10%) of the total shares or voting power of Borrower’s capital stock outstanding before the issuance; provided that the aforementioned percentage shall apply with respect to any one acquisition and all acquisitions in the aggregate per fiscal year and shall be determined as of the date of each such acquisition and such percentages shall be added together for the determination of the aggregate percentage per fiscal year, in each case to the extent that each of the following conditions shall have been satisfied:

- (a) immediately prior to, and after giving effect thereto, no Event of Default shall have occurred and be continuing or would result therefrom;
- (b) all transactions in connection therewith shall be consummated, in all material respects, in accordance with applicable law;
- (c) such acquired Person or assets shall be in the same line of business as is conducted by Borrower as of the Effective Date (or a line of business reasonably related thereto);
- (d) such acquisition shall not cause the focus or locations of Borrower’s and its Subsidiaries’ operations (when taken as a whole) to be located outside of the United States;
- (e) in the case of the purchase or other acquisition of Shares, all of the Shares acquired or otherwise issued by such Person or any newly formed Subsidiary in connection with such acquisition shall be wholly owned by Borrower or a Subsidiary;
- (f) in connection with such acquisition, neither Borrower nor any of its Subsidiaries (including for this purpose, the target of the acquisition) shall acquire or be subject to any Indebtedness or Liens that are not otherwise permitted hereunder;
- (g) Borrower shall have delivered to the Collateral Agent and Lenders at least five (5) Business Days (or such shorter period as may be acceptable to Collateral Agent and Lenders) prior to such proposed acquisition (i) a copy of the purchase agreement related to the proposed acquisition (and any related documents reasonably requested by the Collateral Agent and Lenders), (ii) a general description of the acquired assets or acquired business line or unit or division and the competitive position of such business line or unit or division within the industry, (iii) the sources and uses of funds to finance the proposed acquisition, and (iv) to the extent available, quarterly and annual audited financial statements of the Person whose Shares or assets are being acquired for the twelve (12) month period immediately prior to such proposed acquisition;
- (h) such Permitted Acquisition shall only involve assets located in the United States;
- (i) Collateral Agent and the Lenders have received a certificate from a Responsible Officer together with Board approved projections certifying and setting forth in reasonable detail that Borrower has enough cash on hand to pay its projected expenses and all debt service when due for a period of eighteen (18) months after the consummation of such transaction (after giving effect to such transaction); and
- (j) such Permitted Acquisition shall be consensual and shall have been approved by the target’s board of directors.

Notwithstanding anything to the contrary contained herein, in order for any acquisition of Shares or assets of another Person to constitute a Permitted Acquisition, Borrower must comply with all of the following: (a) within thirty (30) days of the closing of such Permitted Acquisition, the applicable Borrower (or Subsidiary) making such

Permitted Acquisition and the target shall have executed such documents and taken such actions as may be required under Section 6.12; (b) the applicable Borrower shall have delivered to Collateral Agent and Lenders, in form and substance satisfactory to the Collateral Agent and Lenders and sufficiently in advance (and in any case no later than five (5) Business Days prior to such Permitted Acquisition), such other financial information, financial analysis, documentation or other information relating to such Permitted Acquisition and the pro forma certifications required by clause (c) below, in each case, as Collateral Agent and Lenders shall reasonably request; (c) on or prior to the date of such Permitted Acquisition, the Collateral Agent and Lenders shall have received, in form and substance reasonably satisfactory to the Collateral Agent and Lenders, a certificate of the chief financial officer of Borrower certifying compliance with the requirements contained in this definition of "Permitted Acquisition" and with the other terms of the Loan Documents (before and after giving effect to such Permitted Acquisition); and (d) Borrower shall provide to the Collateral Agent and Lenders as soon as available but in any event not later than five (5) Business Days after the execution thereof, a copy of the executed purchase agreement or similar agreement with respect to any such acquisition.

"Permitted Indebtedness" is:

- (a) Borrower's Indebtedness to the Lenders and Collateral Agent under this Agreement and the other Loan Documents;
- (b) Indebtedness existing on the Effective Date and disclosed on the Perfection Certificate(s);
- (c) Subordinated Debt;
- (d) unsecured Indebtedness to trade creditors incurred in the ordinary course of business;

(e) Indebtedness consisting of capitalized lease obligations and purchase money Indebtedness, in each case incurred by Borrower or any of its Subsidiaries to finance the acquisition, repair, improvement or construction of fixed or capital assets of such person, provided that (i) the aggregate outstanding principal amount of all such Indebtedness does not exceed Five Hundred Thousand Dollars (\$500,000.00) at any time and (ii) the principal amount of such Indebtedness does not exceed the lower of the cost or fair market value of the property so acquired or built or of such repairs or improvements financed with such Indebtedness (each measured at the time of such acquisition, repair, improvement or construction is made); furthermore, notwithstanding anything to the contrary herein and strictly for the purposes of this clause (e) of the definition of Permitted Indebtedness and for no other purpose, any obligations of a Person that are or would have been treated as operating leases or capital leases for purposes of GAAP prior to the issuance by the Financial Accounting Standards Board on February 25, 2016 of an Accounting Standards Update (Topic 842) (the "ASU") shall continue to be accounted for as operating leases or capital leases (whether or not such operating lease obligations or capital lease obligations, as applicable, were in effect on such date) notwithstanding the fact that such obligations are required in accordance with the ASU (on a prospective or retroactive basis or otherwise) to be treated as capitalized lease obligations in accordance with GAAP;

- (f) Indebtedness incurred as a result of endorsing negotiable instruments received in the ordinary course of Borrower's business;
- (g) other unsecured Indebtedness in an aggregate amount outstanding at any time not to exceed Two Hundred Fifty Thousand Dollars (\$250,000.00);
- (h) Indebtedness of any Loan Party to any other Loan Party;
- (i) Indebtedness consisting of Investments under clause (f) of the definition of "Permitted Investments";
- (j) Indebtedness relating to insurance premium financing arrangements, not to exceed Two Hundred Fifty Thousand Dollars (\$250,000.00) outstanding at

any time;

(k) any obligations owing with respect to corporate credit cards or merchant services in an aggregate amount outstanding at any time not to exceed Five Hundred Thousand Dollars (\$500,000.00) at any time outstanding;

(l) Indebtedness in respect of letters of credit, bank guarantees, bonds and similar instruments issued for the account of the Borrower or any Subsidiary in the ordinary course of business supporting obligations under (A) workers' compensation, unemployment insurance and other social security laws and (B) bids, trade contracts, leases, statutory obligations, surety and appeal bonds, performance bonds and obligations of a like nature; in an aggregate amount for (A) and (B) not to exceed Five Hundred Thousand Dollars (\$500,000.00) at any time;

(m) Indebtedness of either Borrower and its respective Subsidiaries arising from the honoring by a bank or other financial institution of a check, draft or similar instrument in the ordinary course of business;

(n) Indebtedness representing deferred compensation, severance, pension and health and welfare retirement benefits or the equivalent thereof to current and former employees of either Borrower or its Subsidiaries incurred in the ordinary course of business or in connection with Permitted Investments, not to exceed Five Hundred Thousand Dollars (\$500,000.00) in the aggregate in any fiscal year; and

(o) extensions, refinancings, modifications, amendments and restatements of any items of Permitted Indebtedness (a) through (o) above, provided that the principal amount thereof is not increased or the terms thereof are not modified to impose materially more burdensome terms upon Borrower, or its Subsidiary, as the case may be.

"Permitted Investments" are:

(a) Investments disclosed on the Perfection Certificate(s) and existing on the Effective Date;

(b) (i) Investments consisting of cash and Cash Equivalents, and (ii) any other Investments permitted by Borrower's investment policy, as amended from time to time, provided that such investment policy (and any such amendment thereto) has been approved in writing by Collateral Agent;

(c) Investments consisting of the endorsement of negotiable instruments for deposit or collection or similar transactions in the ordinary course of Borrower;

(d) Investments consisting of Collateral Accounts which Collateral Agent has a perfected security interest to the extent required by Section 6.6;

(e) Investments in connection with Transfers permitted by Section 7.1;

(f) Investments (i) of cash and Cash Equivalents in Syros Securities, so long as an Event of Default does not exist at the time of such Investment and would not exist after giving effect to such Investment and provided that Borrower is, at all times, in compliance with the MSC Investment Conditions, (ii) in non-Loan Party Subsidiaries (other than Syros Securities) not to exceed One Hundred Thousand Dollars (\$100,000.00) in the aggregate in any fiscal year, (iii) by any Loan Party in another Loan Party and (iii) by Subsidiaries in Borrower;

(g) Investments consisting of (i) travel advances and employee relocation loans and other employee loans and advances in the ordinary course of business, and (ii) loans to employees, officers or directors relating to the purchase of equity securities of Borrower or its Subsidiaries pursuant to employee stock purchase plans or agreements approved by Borrower's Board of Directors; not to exceed Two Hundred Fifty Thousand Dollars (\$250,000.00) in the aggregate for (i) and (ii) in any fiscal year;

(h) Investments (including debt obligations) received in connection with the bankruptcy or reorganization of customers or suppliers and in settlement of delinquent obligations of, and other disputes with, customers or suppliers arising in the ordinary course of business;

(i) Investments consisting of notes receivable of, or prepaid royalties and other credit extensions, to customers and suppliers who are not Affiliates, in the ordinary course of business; provided that this paragraph (i) shall not apply to Investments of Borrower in any Subsidiary;

(j) Investments in joint ventures or strategic alliances in the ordinary course of Borrower's business consisting of the non-exclusive licensing of technology, the development of technology or the providing of technical support; provided that any cash Investments by Borrower or its Subsidiaries for such Investments do not exceed Two Hundred Fifty Thousand Dollars (\$250,000.00) in the aggregate in any fiscal year.

(k) the formation or acquisition of Subsidiaries after the Effective Date, subject to compliance with Section 6.12 of this Agreement;

(l) Investments consisting of the conversion or settlement of any convertible securities of Borrower or any Subsidiary or otherwise in exchange therefor;

(m) Permitted Acquisitions, including any investments that are held by acquired Persons acquired pursuant to Permitted Acquisitions, to the extent permitted in accordance with the definition of such term "Permitted Acquisition"; and

(n) other Investments not to exceed Two Hundred Fifty Thousand Dollars (\$250,000.00) in the aggregate in any fiscal year.

"**Permitted Licenses**" are (A) licenses of over-the-counter software that is commercially available to the public, (B) non-exclusive and exclusive licenses for the use of the Intellectual Property of Borrower or any of its Subsidiaries entered into in the ordinary course of business, provided, that, with respect to each such license described in clause (B), (i) no Event of Default has occurred or is continuing at the time of such license; (ii) the license constitutes an arms-length transaction, the terms of which, on their face, do not provide for a sale or assignment of any Intellectual Property and do not restrict the ability of Borrower or any of its Subsidiaries, as applicable, to pledge, grant a security interest in or lien on, or assign or otherwise Transfer any Intellectual Property; (iii) in the case of any exclusive license, (x) Borrower delivers ten (10) days' prior written notice and a brief summary of the terms of the proposed license to Collateral Agent and the Lenders and delivers to Collateral Agent and the Lenders copies of the final executed licensing documents in connection with the exclusive license promptly upon consummation thereof, and (y) any such license could not result in a legal transfer of title of the licensed property but may be exclusive in respects other than territory and may be exclusive as to territory only as to discrete geographical areas outside of the

United States; and (iv) all upfront payments, royalties, milestone payments or other proceeds arising from the licensing agreement that are payable to Borrower or any of its Subsidiaries are paid to a Deposit Account that is governed by a Control Agreement, and (C) any licenses pursuant to the GBT Agreement or the Incyte Agreement, including licenses the Borrower is obligated to grant pursuant to the GBT Agreement or the Incyte Agreement.

"**Permitted Liens**" are:

(a) Liens existing on the Effective Date and disclosed on the Perfection Certificates or arising under this Agreement and the other Loan Documents;

(b) Liens for taxes, fees, assessments or other government charges or levies, either (i) not due and payable or (ii) being contested in good faith and for which Borrower maintains adequate reserves on its Books, provided that no notice of any such Lien has been filed or recorded under the Internal Revenue Code of 1986, as amended, and the Treasury Regulations adopted thereunder;

(c) liens securing Indebtedness permitted under clause (c) of the definition of "**Permitted Indebtedness**," provided that (i) such Liens exist prior to the acquisition of, or attach substantially simultaneous with, or within twenty (20) days after the, acquisition, lease, repair, improvement or construction of, such property financed or leased by such Indebtedness and (ii) such liens do not extend to any property of Borrower other than the property (and proceeds thereof) acquired, leased or built, or the improvements or repairs, financed by such Indebtedness;

(d) Liens securing claims or demands of materialmen, mechanics, carriers, warehousemen, landlords and suppliers, or other Persons that are possessory in nature arising in the ordinary course of business so long as such Liens attach only to Inventory, securing liabilities in the aggregate amount of the obligations secured by such

Liens does not exceed Two Hundred Fifty Thousand Dollars (\$250,000.00), and which are not delinquent or remain payable without penalty or which are being contested in good faith and by appropriate proceedings which proceedings have the effect of preventing the forfeiture or sale of the property subject thereto;

(e) Liens to secure payment of workers' compensation, employment insurance, old-age pensions, social security and other like obligations incurred in the ordinary course of business (other than Liens imposed by ERISA);

(f) leases or subleases of real property granted in the ordinary course of Borrower's business (or, if referring to another Person, in the ordinary course of such Person's business), and leases, subleases, non-exclusive licenses or sublicenses of personal property (other than Intellectual Property) granted in the ordinary course of Borrower's business (or, if referring to another Person, in the ordinary course of such Person's business), if the leases, subleases, licenses and sublicenses do not prohibit granting Collateral Agent or any Lender a security interest therein;

(g) banker's liens, rights of setoff and Liens in favor of financial institutions incurred in the ordinary course of business arising in connection with Borrower's deposit accounts or securities accounts held at such institutions solely to secure payment of fees and similar costs and expenses and provided such accounts are maintained in compliance with Section 6.6(b) hereof;

(h) Liens arising from judgments, decrees or attachments in circumstances not constituting an Event of Default under Section 8.4 or 8.7;

(i) Liens consisting of Permitted Licenses;

(j) deposits to secure the performance of leases entered into in the ordinary course of business and not representing an obligation for borrowed money so long as (i) each such deposit is made at the commencement of a lease or its renewal when there is no underlying default under such lease and (ii) the aggregate amount of all such outstanding deposits does not exceed Two Hundred Fifty Thousand Dollars (\$250,000.00);

(k) easements, reservations, rights-of-way, restrictions, minor defects or irregularities in title and other similar Liens affecting Borrower's owned real property not interfering in any material respect with the ordinary course of Borrower's business;

(l) deposits to secure Indebtedness permitted by clause (l) of the definition of "Permitted Indebtedness" or the performance of bids, trade contracts (other than for borrowed money), contracts for the purchase of property permitted hereunder, statutory obligations, surety and appeal bonds, performance bonds and other obligations of a like nature; in each case, incurred in the ordinary course of business;

(m) Liens granted in the ordinary course of business in connection with the financing of insurance premiums securing Indebtedness permitted by clause (j) of the definition of "Permitted Indebtedness"; and

(n) Liens incurred in the extension, renewal or refinancing of the Indebtedness secured by Liens described in (a) through (n), but any extension, renewal or replacement Lien must be limited to the property encumbered by the existing Lien and the principal amount of the Indebtedness may not increase.

"**Person**" is any individual, sole proprietorship, partnership, limited liability company, joint venture, company, trust, unincorporated organization, association, corporation, institution, public benefit corporation, firm, joint stock company, estate, entity or government agency.

"**Post Closing Letter**" is that certain Post Closing Letter dated as of the Effective Date by and between Collateral Agent and Borrower.

"**Prepayment Fee**" is, with respect to any Term Loan subject to prepayment prior to the Maturity Date, whether by mandatory or voluntary prepayment, acceleration or otherwise, an additional fee payable to the Lenders in amount equal to:

(i) for a prepayment made on or after the Funding Date of such Term Loan through and including the first anniversary of the Funding Date of such Term Loan, two percent (2.00%) of the principal amount of such Term Loan prepaid;

(ii) for a prepayment made after the date which is after the first anniversary of the Funding Date of such Term Loan through and including the second anniversary of the Funding Date of such Term Loan, one percent (1.00%) of the principal amount of the Term Loans prepaid; and

(iii) for a prepayment made after the date which is after the second anniversary of the Funding Date of such Term Loan and prior to the Maturity Date, one half percent (0.50%) of the principal amount of the Term Loans prepaid.

“Pro Rata Share” is, as of any date of determination, with respect to each Lender, a percentage (expressed as a decimal, rounded to the ninth decimal place) determined by dividing the outstanding principal amount of Term Loans held by such Lender by the aggregate outstanding principal amount of all Term Loans.

“Registered Organization” is any “registered organization” as defined in the Code with such additions to such term as may hereafter be made.

“Required Lenders” means (i) for so long as all of the Persons that are Lenders on the Effective Date (each an **“Original Lender”**) have not assigned or transferred any of their interests in their Term Loan, Lenders holding one hundred percent (100%) of the aggregate outstanding principal balance of the Term Loan, or (ii) at any time from and after any Original Lender has assigned or transferred any interest in its Term Loan, Lenders holding at least sixty six percent (66%) of the aggregate outstanding principal balance of the Term Loan and, in respect of this clause (ii), (A) each Original Lender that has not assigned or transferred any portion of its Term Loan, (B) each assignee or transferee of an Original Lender’s interest in the Term Loan, but only to the extent that such assignee or transferee is an Affiliate or Approved Fund of such Original Lender, and (C) any Person providing financing to any Person described in clauses (A) and (B) above; provided, however, that this clause (C) shall only apply upon the occurrence of a default, event of default or similar occurrence with respect to such financing.

“Requirement of Law” is as to any Person, the organizational or governing documents of such Person, and any law (statutory or common), treaty, rule or regulation or determination of an arbitrator or a court or other Governmental Authority, in each case applicable to or binding upon such Person or any of its property or to which such Person or any of its property is subject.

“Responsible Officer” is any of the President, Chief Executive Officer, or Chief Financial Officer of Borrower acting alone.

“Secured Promissory Note” is defined in Section 2.4.

“Secured Promissory Note Record” is a record maintained by each Lender with respect to the outstanding Obligations owed by Borrower to Lender and credits made thereto.

“Securities Account” is any “securities account” as defined in the Code with such additions to such term as may hereafter be made.

“Shares” is one hundred percent (100%) of the issued and outstanding capital stock, membership units or other securities owned or held of record by Borrower or Borrower’s Subsidiary, in any Subsidiary.

“Solvent” is, with respect to any Person: the fair salable value of such Person’s consolidated assets (including goodwill minus disposition costs) exceeds the fair value of such Person’s liabilities; such Person is not left with unreasonably small capital after the transactions in this Agreement; and such Person is able to pay its debts (including trade debts) as they mature.

“Subordinated Debt” is Indebtedness incurred by Borrower or any of its Subsidiaries subordinated to all Indebtedness of Borrower and/or its Subsidiaries to the Lenders (pursuant to a subordination, intercreditor, or other similar agreement in form and substance satisfactory to Collateral Agent and the Lenders entered into between

Collateral Agent, Borrower, and/or any of its Subsidiaries, and the other creditor), on terms acceptable to Collateral Agent and the Lenders.

“**Subsidiary**” is, with respect to any Person, any Person of which more than fifty percent (50%) of the voting stock or other equity interests (in the case of Persons other than corporations) is owned or controlled, directly or indirectly, by such Person or through one or more intermediaries.

“**Syros Ireland**” means Syros Pharmaceuticals Limited, a wholly owned Subsidiary of Borrower organized under the laws of Ireland.

“**Syros Securities**” means Syros Securities Corporation, a Massachusetts corporation and wholly owned Subsidiary of Borrower.

“**Term A Loan**” is defined in Section 2.2(a)(i) hereof.

“**Term B Loan**” is defined in Section 2.2(a)(ii) hereof.

“**Term B Draw Period**” is the period commencing on the date of the occurrence of the Term B Milestone and ending on the earlier of (i) the date which is thirty (30) days after the date the Term B Milestone is achieved, (ii) March 31, 2021 and (iii) the occurrence of an Event of Default; provided, however, that the Term B Draw Period shall not commence if on the date of the occurrence of the Term B Milestone an Event of Default has occurred and is continuing.

“**Term B Milestone**” means Borrower’s achievement of positive data from the cohort in relapsed/refractory AML patients in connection with Borrower’s SY-1425 Phase 2 trial program in combination with azacitidine; provided that Borrower has provided to Collateral Agent written evidence of the same, in form and content acceptable to Collateral Agent in its sole discretion.

“**Term C Loan**” is defined in Section 2.2(a)(iii) hereof.

“**Term Loan**” is defined in Section 2.2(a)(iii) hereof.

“**Term Loan Commitment**” is, for any Lender, the obligation of such Lender to make a Term Loan, up to the principal amount shown on Schedule 1.1. “**Term Loan Commitments**” means the aggregate amount of such commitments of all Lenders.

“**Trademarks**” means any trademark and servicemark rights, whether registered or not, applications to register and registrations of the same and like protections, and the entire goodwill of the business of Borrower connected with and symbolized by such trademarks.

“**Transfer**” is defined in Section 7.1.

“**Warrants**” are those certain Warrants to Purchase Stock dated as of the Effective Date, or any date thereafter, issued by Borrower in favor of each Lender or such Lender’s Affiliates.

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IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed as of the Effective Date.

BORROWER:

SYROS PHARMACEUTICALS, INC.

By: /s/ Joseph J. Ferra, Jr.
Name: Joseph J. Ferra, Jr.
Title: Chief Financial Officer

COLLATERAL AGENT AND LENDER:

OXFORD FINANCE LLC

By: /s/ Colette H. Featherly
Name: Colette H. Featherly
Title: Senior Vice President

[Signature Page to Loan and Security Agreement]

SCHEDULE 1.1

Lenders and Commitments

Term A Loan

| Lender | Term Loan Commitment | Commitment Percentage |
|--------------------|----------------------|-----------------------|
| OXFORD FINANCE LLC | \$ 20,000,000.00 | 100.00 % |
| TOTAL | \$ 20,000,000.00 | 100.00 % |

Term B Loans

| Lender | Term Loan Commitment | Commitment Percentage |
|--------------------|----------------------|-----------------------|
| OXFORD FINANCE LLC | \$ 20,000,000.00 | 100.00 % |
| TOTAL | \$ 20,000,000.00 | 100.00 % |

Aggregate (all Term Loans)

| Lender | Term Loan Commitment | Commitment Percentage |
|--------------------|----------------------|-----------------------|
| OXFORD FINANCE LLC | \$ 40,000,000.00 | 100.00 % |
| TOTAL | \$ 40,000,000.00 | 100.00 % |

EXHIBIT A

Description of Collateral

The Collateral consists of all of Borrower's right, title and interest in and to the following personal property:

All goods, Accounts (including health-care receivables), Equipment, Inventory, contract rights or rights to payment of money, leases, license agreements, franchise agreements, General Intangibles (except as noted below), commercial tort claims, documents, instruments (including any promissory notes), chattel paper (whether tangible or electronic), cash, deposit accounts and other Collateral Accounts, all certificates of deposit, fixtures, letters of credit rights (whether or not the letter of credit is evidenced by a writing), securities, and all other investment property, supporting obligations, and financial assets, whether now owned or hereafter acquired, wherever located; and

All Borrower's Books relating to the foregoing, and any and all claims, rights and interests in any of the above and all substitutions for, additions, attachments, accessories, accessions and improvements to and replacements, products, proceeds and insurance proceeds of any or all of the foregoing.

Notwithstanding the foregoing, the Collateral does not include (i) any Intellectual Property; provided, however, the Collateral shall include all Accounts and all proceeds of Intellectual Property. If a judicial authority (including a U.S. Bankruptcy Court) would hold that a security interest in the underlying Intellectual Property is necessary to have a security interest in such Accounts and such property that are proceeds of Intellectual Property, then the Collateral shall automatically, and effective as of the Effective Date, include the Intellectual Property to the extent necessary to permit perfection of Collateral Agent's security interest in such Accounts and such other property of Borrower that are proceeds of the Intellectual Property; and (ii) any license or contract, in each case if the granting of a Lien in such license or contract is prohibited by or would constitute a default under the agreement governing such license or contract (but (A) only to the extent such prohibition is enforceable under applicable law and (B) other than to the extent that any such term would be rendered ineffective pursuant to Sections 9-406, 9-408 or 9-409 (or any other Section) of Division 9 of the Code); provided that upon the termination, lapsing or expiration of any such prohibition, such license or contract, as applicable, shall automatically be subject to the security interest granted in favor of Collateral Agent hereunder and become part of the "Collateral."

Pursuant to the terms of a certain negative pledge arrangement with Collateral Agent and the Lenders, Borrower has agreed not to encumber any of its Intellectual Property.

EXHIBIT B

Form of Disbursement Letter

[see attached]

DISBURSEMENT LETTER

February 12, 2020

The undersigned, being the duly elected and acting _____ of SYROS PHARMACEUTICALS, INC., a Delaware corporation with offices located at 35 CambridgePark Drive, Cambridge, MA 02140 (“**Borrower**”), does hereby certify to **OXFORD FINANCE LLC** (“**Oxford**” and “**Lender**”), as collateral agent (the “**Collateral Agent**”) in connection with that certain Loan and Security Agreement dated as of February 12, 2020, by and among Borrower, Collateral Agent and the Lenders from time to time party thereto (the “**Loan Agreement**”; with other capitalized terms used below having the meanings ascribed thereto in the Loan Agreement) that:

1. The representations and warranties made by Borrower in Section 5 of the Loan Agreement and in the other Loan Documents are true and correct in all material respects as of the date hereof.
2. No event or condition has occurred that would constitute an Event of Default under the Loan Agreement or any other Loan Document.
3. Borrower is in compliance with the covenants and requirements contained in Sections 4, 6 and 7 of the Loan Agreement.
4. All conditions referred to in Section 3 of the Loan Agreement to the making of the Loan to be made on or about the date hereof have been satisfied or waived by Collateral Agent.
5. No Material Adverse Change has occurred.
6. The undersigned is a Responsible Officer.
7. The proceeds of the Term A Loan shall be disbursed as follows:

| | |
|---|------------------|
| Disbursement from Oxford: | |
| Loan Amount | \$ _____ |
| Plus: | |
| —Deposit Received | [\$ 50,000.00] |
| Less: | |
| —Facility Fee | (\$ 100,000.00) |
| [—Interim Interest | (\$)] |
| —Lender’s Legal Fees | (\$)* |
| TOTAL TERM A LOAN NET PROCEEDS FROM OXFORD | \$ _____ |

8. The Term A Loan shall amortize in accordance with the Amortization Table attached hereto.
9. The aggregate net proceeds of the Term Loans shall be transferred to the Designated Deposit Account as follows:

| | |
|-----------------|-----------------------------|
| Account Name: | SYROS PHARMACEUTICALS, INC. |
| Bank Name: | Silicon Valley Bank |
| Bank Address: | [] |
| Account Number: | [] |
| ABA Number: | [] |

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Dated as of the date first set forth above.

BORROWER:

SYROS PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____

COLLATERAL AGENT AND LENDER:

OXFORD FINANCE LLC

By _____

Name: _____

Title: _____

[Signature Page to Disbursement Letter]

AMORTIZATION TABLE
(Term A Loan)

[see attached]

EXHIBIT C

Compliance Certificate

TO: OXFORD FINANCE LLC, as Collateral Agent and Lender

FROM: SYROS PHARMACEUTICALS, INC.

The undersigned authorized officer (“**Officer**”) of SYROS PHARMACEUTICALS, INC. (“**Borrower**”), hereby certifies that in accordance with the terms and conditions of the Loan and Security Agreement by and among Borrower, Collateral Agent, and the Lenders from time to time party thereto (as amended, restated, supplemented or otherwise modified from time to time, the “**Loan Agreement**,” capitalized terms used but not otherwise defined herein shall have the meanings given them in the Loan Agreement),

(a) Borrower is in complete compliance for the period ending with all required covenants except as noted below;

(b) There are no Events of Default, except as noted below;

(c) Except as noted below, all representations and warranties of Borrower stated in the Loan Documents are true and correct in all material respects on this date and for the period described in (a), above; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true, accurate and complete in all material respects as of such date.

(d) Borrower, and each of Borrower’s Subsidiaries, has timely filed all required tax returns and reports or extension thereof, Borrower, and each of Borrower’s Subsidiaries, has timely paid all foreign, federal, state, and local taxes, assessments, deposits and contributions owed by Borrower, or Subsidiary, except as otherwise permitted pursuant to the terms of Section 5.8 of the Loan Agreement;

(e) No Liens have been levied or claims made against Borrower or any of its Subsidiaries relating to unpaid employee payroll or benefits of which Borrower has not previously provided written notification to Collateral Agent and the Lenders.

Attached are the required documents, if any, supporting our certification(s). The Officer, on behalf of Borrower, further certifies that the attached financial statements are prepared in accordance with Generally Accepted Accounting Principles (GAAP) and are consistently applied from one period to the next except as explained in an accompanying letter or footnotes and except, in the case of unaudited financial statements, for the absence of footnotes and subject to year-end audit adjustments as to the interim financial statements.

Please indicate compliance status since the last Compliance Certificate by circling Yes, No, or N/A under “Complies” column.

| | Reporting Covenant | Requirement | Actual | Complies | | |
|----|--|---|--------|----------|----|-----|
| 1) | Financial statements and month-end account statements for each Collateral Account | Monthly within 30 days; Quarterly within 45 days | | Yes | No | N/A |
| 2) | Annual (CPA Audited) statements | Within 120 days after FYE | | Yes | No | N/A |
| 3) | Annual Financial Projections/Budget (prepared on a monthly basis) | Annually (within 60 days of FYE), and when revised | | Yes | No | N/A |
| 4) | 8-K, 10-K and 10-Q Filings | Upon filing and if otherwise applicable, within 5 Business Days of filing | | Yes | No | N/A |
| 5) | Compliance Certificate | Monthly within 30 days; quarterly within 45 days | | Yes | No | N/A |
| 6) | Total amount of Borrower’s cash and cash equivalents at the last day of the measurement period | | \$ | Yes | No | N/A |
| 7) | Total amount of Borrower’s Subsidiaries’ cash and cash equivalents at the last day of the measurement period | | \$ | Yes | No | N/A |

Deposit and Securities Accounts

(Please list all accounts; attach separate sheet if additional space needed)

| | Institution Name | Account Number | New Account? | | Account Control Agreement in place? | |
|----|------------------|----------------|--------------|----|-------------------------------------|----|
| 1) | | | Yes | No | Yes | No |
| 2) | | | Yes | No | Yes | No |
| 3) | | | Yes | No | Yes | No |
| 4) | | | Yes | No | Yes | No |

MSC Investment Condition (please attached a separate sheet showing detailed calculations)

| | | |
|--------------------------------------|--|----|
| 1) Account Balance (subject to ACAs) | Note less than the lesser of (i) One Hundred Ten percent (110.00%) of the aggregate principal amount of outstanding Term Loans and (ii) the amount of Borrower’s and all of its Subsidiaries’ aggregate consolidated cash and Cash Equivalent assets | \$ |
|--------------------------------------|--|----|

Other Matters

| | | | |
|-----|---|-----|----|
| 1. | Has a Key Person ceased to be actively engaged in the management of Borrower since the last Compliance Certificate (see Section 7.2(c))? | Yes | No |
| 2. | Have there been any transfers/sales/disposals/retirement of Collateral or IP prohibited by the Loan Agreement? | Yes | No |
| 3. | Have there been any new or pending or threatened (in writing) claims or causes of action by or against Borrower that involve more than Two Hundred Fifty Thousand Dollars (\$250,000.00), or has Borrower acquired a commercial tort claims with a value in excess of Fifty Thousand Dollars (\$50,000.00)? If yes, please provide details (see Section 4.1 and Section 6.9). | Yes | No |
| 4. | Has Borrower nor any of its Subsidiaries become party to or bound by any license or agreement with respect to which Borrower or any Subsidiary is the licensee (other than (x) over the counter software that is commercially available to the public, and (y) non-exclusive licenses (i) from research and development vendors, academic institutions and clinical trial sites entered into in the ordinary course of business, (ii) on a form substantially conforming with Borrower's form master services agreement, material transfer agreement or vendor contract, each as provided to Collateral Agent and each Lender entered into in the ordinary course of business, and (iii) from service providers of Borrower providing corporate sponsorship and/or promotional items, auditing and accounting services, human resources support services, non-proprietary information technology software, and market research entered into in the ordinary course of business, the principal purposes of which do not include the acquisition of licensing rights, but which contain such non-exclusive licenses merely ancillary to, and for the limited purposes of facilitating, the principal purposes of the agreement, in each case so long as Borrower has complied with all other applicable terms of the Loan Documents applicable thereto) (see Section 5.2(d)). | Yes | No |
| 5. | Have any material Governmental Approvals obtained by Borrower or any of its Subsidiaries (see Section 6.1(b)). If yes, please provide copies. | Yes | No |
| 6. | Have there been revisions to the Annual Projections that have not been delivered to each Lender (see Section 6.2(a)(iii))? If yes, please provide copies. | Yes | No |
| 7. | Have there been any amendments of or other changes to the Operating Documents of Borrower or any of its Subsidiaries (see Section 6.2(a)(vi))? If yes, provide copies of any such amendments or changes with this Compliance Certificate. | Yes | No |
| 8. | Has any event occurred that could reasonably be expected to materially and adversely affect the value of the Intellectual Property (see Section 6.2(a)(vii)). If yes, please provide details. | Yes | No |
| 9. | Has there been any returns, recoveries, disputes or claims that involve Inventory with a book value of more than Two Hundred Fifty Thousand Dollars (\$250,000.00) individually or in the aggregate (see Section 6.3). If yes, please provide details. | Yes | No |
| 10. | Has there been a material infringement by a third party of the Intellectual Property of the Borrower or its Subsidiaries (see Section 6.7). If yes, please provide details. | Yes | No |

Exceptions

Please explain any exceptions with respect to the certification above: (If no exceptions exist, state “No exceptions.” Attach separate sheet if additional space needed.)

SYROS PHARMACEUTICALS, INC.

By _____

Name: _____

Title: _____

Date:

LENDER USE ONLY

Received by:

Date:

Verified by:

Date:

Compliance Status: Yes No

EXHIBIT D

Form of Secured Promissory Note

[see attached]

SECURED PROMISSORY NOTE
(Term [A][B][C] Loan)

§

Dated: February , 2020

FOR VALUE RECEIVED, the undersigned, SYROS PHARMACEUTICALS, INC., a Delaware corporation with offices located at 35 CambridgePark Drive, Cambridge, MA 02140 ("**Borrower**") HEREBY PROMISES TO PAY to the order of OXFORD FINANCE LLC ("**Lender**") the principal amount of [] MILLION DOLLARS (\$) or such lesser amount as shall equal the outstanding principal balance of the Term [A][B][C] Loan made to Borrower by Lender, plus interest on the aggregate unpaid principal amount of such Term [A][B][C] Loan, at the rates and in accordance with the terms of the Loan and Security Agreement dated February , 2020 by and among Borrower, Lender, Oxford Finance LLC, as Collateral Agent, and the other Lenders from time to time party thereto (as amended, restated, supplemented or otherwise modified from time to time, the "**Loan Agreement**"). If not sooner paid, the entire principal amount and all accrued and unpaid interest hereunder shall be due and payable on the Maturity Date as set forth in the Loan Agreement. Any capitalized term not otherwise defined herein shall have the meaning attributed to such term in the Loan Agreement.

Principal, interest and all other amounts due with respect to the Term [A][B][C] Loan, are payable in lawful money of the United States of America to Lender as set forth in the Loan Agreement and this Secured Promissory Note (this "**Note**"). The principal amount of this Note and the interest rate applicable thereto, and all payments made with respect thereto, shall be recorded by Lender and, prior to any transfer hereof, endorsed on the grid attached hereto which is part of this Note.

The Loan Agreement, among other things, (a) provides for the making of a secured Term [A][B][C] Loan by Lender to Borrower, and (b) contains provisions for acceleration of the maturity hereof upon the happening of certain stated events.

This Note may not be prepaid except as set forth in Section 2.2 (c) and Section 2.2(d) of the Loan Agreement.

This Note and the obligation of Borrower to repay the unpaid principal amount of the Term [A][B][C] Loan, interest on the Term [A][B][C] Loan and all other amounts due Lender under the Loan Agreement is secured under the Loan Agreement.

Presentment for payment, demand, notice of protest and all other demands and notices of any kind in connection with the execution, delivery, performance and enforcement of this Note are hereby waived.

Borrower shall pay all reasonable fees and expenses, including, without limitation, reasonable attorneys' fees and costs, incurred by Lender in the enforcement or attempt to enforce any of Borrower's obligations hereunder not performed when due.

This Note shall be governed by, and construed and interpreted in accordance with, the internal laws of the State of New York.

The ownership of an interest in this Note shall be registered on a record of ownership maintained by Lender or its agent. Notwithstanding anything else in this Note to the contrary, the right to the principal of, and stated interest on, this Note may be transferred only if the transfer is registered on such record of ownership and the transferee is identified as the owner of an interest in the obligation. Borrower shall be entitled to treat the registered holder of this Note (as recorded on such record of ownership) as the owner in fact thereof for all purposes and shall not be bound to recognize any equitable or other claim to or interest in this Note on the part of any other person or entity.

[Balance of Page Intentionally Left Blank]

IN WITNESS WHEREOF, Borrower has caused this Note to be duly executed by one of its officers thereunto duly authorized on the date hereof.

BORROWER:

SYROS PHARMACEUTICALS, INC.

By _____

Name: _____

Title: _____

LOAN INTEREST RATE AND PAYMENTS OF PRINCIPAL

| Date | Principal Amount | Interest Rate | Scheduled Payment Amount | Notation By |
|------|------------------|---------------|--------------------------|-------------|
| | | | | |
| | | | | |
| | | | | |

FIRST AMENDMENT TO LOAN AND SECURITY AGREEMENT

THIS FIRST AMENDMENT TO LOAN AND SECURITY AGREEMENT (this “**Amendment**”) is entered into as of July 3, 2022, by and among OXFORD FINANCE LLC, a Delaware limited liability company with an office located at 115 South Union Street, Suite 300, Alexandria, Virginia 22314 (“**Oxford**”), as collateral agent (in such capacity, “**Collateral Agent**”), the Lenders listed on Schedule 1.1 to the Loan Agreement (as defined below) or otherwise a party thereto from time to time including Oxford in its capacity as a Lender (each a “**Lender**” and collectively, the “**Lenders**”), and SYROS PHARMACEUTICALS, INC., a Delaware corporation with offices located at 840 Memorial Drive, Cambridge, MA 02139 (“**Borrower**”).

A. Collateral Agent, Borrower and Lenders have entered into that certain Loan and Security Agreement dated as of February 12, 2020 (as amended, supplemented or otherwise modified from time to time, the “**Loan Agreement**”) pursuant to which Lenders have provided to Borrower certain loans in accordance with the terms and conditions thereof;

B. Borrower, Tack Acquisition Corp., a Delaware corporation and a wholly owned Subsidiary of Borrower (“**Merger Sub**”) and Tyme Technologies, Inc. (“**Merger Partner**”), a Delaware corporation are entering into that certain Agreement and Plan of Merger (in the form attached hereto as Exhibit A, and as may be amended to the extent permitted by Section 2.1 hereof only, the “**Merger Agreement**”) on July 3, 2022 pursuant to which Borrower and Merger Partner will enter into a business combination transaction and Merger Partner will become a wholly owned subsidiary of Borrower.

C. Sections 7.2(c)(ii)(y) and 7.3 of the Loan Agreement require Borrower to obtain the consent of the Required Lenders to enter into the Merger Agreement and consummate the transactions contemplated thereby and Borrower has asked Collateral Agent and the Required Lenders to provide such consent;

D. Collateral Agent and the Required Lenders have agreed to (i) provide consent to Borrower entering into the Merger Agreement and consummating the transactions contemplated thereby and (ii) amend certain provisions of the Loan Agreement, subject to, and in accordance with, the terms and conditions set forth herein, and in reliance upon the representations and warranties set forth herein.

AGREEMENT

NOW, THEREFORE, in consideration of the promises, covenants and agreements contained herein, and other good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, Borrower, the Required Lenders and Collateral Agent hereby agree as follows:

1. Definitions. Capitalized terms used but not defined in this Amendment shall have the meanings given to them in the Loan Agreement.

2. Consent.

2.1 Subject to the terms and conditions hereof, including Section 2.2 hereof, Collateral Agent and the Required Lenders hereby consent to Borrower’s execution, delivery and performance of the Merger Agreement and consummating the Merger (as defined in the Merger Agreement) and other transactions contemplated thereby; provided, however, (a) any amendment or waiver of the Merger Agreement, including any amendment of any exhibit or schedule thereto, that would either (i) adversely affect the Lenders or (ii) materially and adversely affect Borrower, shall be subject to the prior written approval of Collateral Agent and the Required Lenders and (b) at all times prior to consummating the Merger, Borrower shall not (i) Transfer to, license to or permit Merger Sub to hold any Intellectual Property and (ii) Transfer or permit Merger Sub to hold any assets having an aggregate value in excess of Ten Thousand Dollars (\$10,000.00).

2.2 The consent of Collateral Agent and the Lenders to the consummation of the Merger, is subject to Borrower’s satisfaction of the following conditions:

(a) immediately prior to the Merger, and after giving effect to the Merger, no Event of Default shall have occurred and be continuing or would result therefrom;

(b) the Merger shall be consummated, in all material respects, in accordance with applicable law and the terms of the Merger Agreement and no closing condition set forth in Section 7.1 and Section 7.2 of the Merger Agreement shall have been waived by Borrower or Merger Sub, without the prior written approval of Collateral Agent and the Required Lenders;

(c) upon consummation of the Merger, Merger Partner shall become a wholly owned Subsidiary of Borrower;

(d) in connection with the Merger, neither Borrower nor any of its Subsidiaries (including for this purpose, Merger Partner or any of its Subsidiaries (if any)) shall acquire or be subject to any Indebtedness or Liens that are not otherwise permitted by the Loan Agreement;

(e) the Merger shall be consensual and shall have been approved by Merger Partner's board of directors; and

(f) on the date of the Merger (but immediately prior to the consummation of the Merger), the Collateral Agent and Lenders shall have received a certificate of the chief financial officer of Borrower in the form attached hereto as Exhibit B certifying compliance with the requirements contained in this Section 2.2 (both before and after giving effect to the Merger).

3. Amendments to Loan Agreement.

3.1 Section 10 (Notices). Section 10 of the Loan Agreement is amended by replacing the address for notices to Collateral Agent (but not the address for a courtesy copy for Collateral Agent) with the following:

“OXFORD FINANCE LLC
115 South Union Street, Suite 300
Alexandria, VA 22314
Attention: Legal Department
Fax: (703) 519-5225
Email: LegalDepartment@oxfordfinance.com”

3.2 Section 2.5 (Fees). Section 2.5 is amended by (a) deleting the word “and” at the end of clause (d), (b) replacing the period at the end of clause (e) with a semicolon, and (c) adding the following new clause (f) to immediately follow clause (e):

“(f) Interest-Only Extension Milestone Fees. The First Interest-Only Extension Milestone Fee, when due hereunder, to be shared between the Lenders in accordance with their respective Pro Rata Shares and the Second Interest-Only Extension Milestone Fee, when due hereunder, to be shared between the Lenders in accordance with their respective Pro Rata Shares.”

3.3 Section 13 (Definitions). The following defined terms in Section 13 of the Loan Agreement are amended and restated as follows:

“**Amortization Date**” is, March 1, 2023; provided, however, (a) if Borrower achieves the First Interest-Only Extension Milestone prior to January 1, 2023, then the Amortization Date with respect to all Term Loans shall automatically be extended to March 1, 2024, and (b) if the Amortization Date is March 1, 2024 and Borrower achieves the Second Interest-Only Milestone prior to January 1, 2024, then the Amortization Date with respect to all Term Loans shall automatically be extended to September 1, 2024.

“**Key Person**” is each of Borrower's (i) Chief Executive Officer, who is Nancy Simonian as of the Effective Date and (ii) Chief Financial Officer, who is Jason Haas as of the First Amendment Effective Date.

“**Maturity Date**” is (a) February 1, 2025, if the Amortization Date is March 1, 2023, (b) February 1, 2026, if the Amortization Date is March 1, 2024 and (c) August 1, 2026 if the Amortization Date is September 1, 2024.

“Obligations” are all of Borrower’s obligations to pay when due any debts, principal, interest, Lenders’ Expenses, the Prepayment Fee, the Final Payment, the First Interest-Only Extension Milestone Fee, the Second Interest-Only Extension Milestone Fee, and other amounts Borrower owes the Lenders now or later, in connection with, related to, following, or arising from, out of or under, this Agreement or, the other Loan Documents (other than the Warrants), or otherwise, and including interest accruing after Insolvency Proceedings begin (whether or not allowed) and debts, liabilities, or obligations of Borrower assigned to the Lenders and/or Collateral Agent, and the performance of Borrower’s duties under the Loan Documents (other than the Warrants).

3.4 Section 13 (Definitions). The following defined terms is added to Section 13 of the Loan Agreement in appropriate alphabetical order:

“First Amendment Effective Date” means July 3, 2022.

“First Amendment to Loan Agreement” means that certain First Amendment to Loan and Security Agreement dated as of July 3, 2022 by and among among Collateral Agent, Borrower and Lenders.

“First Interest-Only Extension Milestone” means Borrower’s delivery to Collateral Agent and Lenders of (a) evidence, satisfactory to Collateral Agent and Lenders in their sole discretion, that (i) Borrower has acquired Tyme Technologies, Inc. pursuant to the terms of the Merger Agreement and the Merger Partner Net Cash (excluding, the amount by which such Merger Partner Net Cash was increased for any Litigation Losses) as of the Closing Date (as such terms are defined in the Merger Agreement) is at least Fifty Million Dollars (\$50,000,000.00) and (ii) Borrower has received net unrestricted (other than Liens imposed pursuant to this Agreement) proceeds from the sale of Borrower’s equity securities or equity-linked securities of at least Ninety Million Dollars (\$90,000,000.00) from a private investment in public equity offering pursuant to that certain Securities Purchase Agreement, dated as of July 3, 2022, by and among the investors identified on Exhibit A attached thereto and their Affiliates or such other investors satisfactory to Collateral Agent and Lenders in their reasonable discretion, and (b) Borrower’s written election to pay the First Interest-Only Extension Milestone Fee either (i) within five (5) Business Days of confirmation from Collateral Agent that the Amortization Date is March 1, 2024 or (ii) upon the earliest to occur of (A) the Maturity Date, (B) the acceleration of any Term Loan, or (C) the prepayment of any Term Loan pursuant to Section 2.2(c) or (d).

“First Interest-Only Extension Milestone Fee” means a fee, due and payable to Lenders in accordance with their respective Pro Rata Shares if the Amortization Date is March 1, 2024, in the aggregate amount equal to: (a) if Borrower has elected to pay such fee within five (5) Business Days of confirmation from Collateral Agent that the Amortization Date is March 1, 2024, Three Hundred Thousand Dollars (\$300,000.00), or (b) if Borrower has elected to pay such fee upon the earliest to occur of (A) the Maturity Date, (B) the acceleration of any Term Loan, or (C) the prepayment of any Term Loan pursuant to Section 2.2(c) or (d), Seven Hundred Twenty-Five Thousand Dollars (\$725,000.00).

“Merger Agreement” means that certain Agreement and Plan of Merger by and among Borrower, Tack Acquisition Corp., a Delaware corporation and a wholly owned Subsidiary of Borrower, and Tyme Technologies, Inc., a Delaware corporation, dated as of July 3, 2022, as amended to the extent permitted by Section 2.1 of the First Amendment to Loan Agreement.

“Second Interest-Only Extension Milestone” means Borrower’s delivery to Collateral Agent and Lenders of (a) evidence, satisfactory to Collateral Agent and Lenders in their sole discretion, that Borrower has either (i) enrolled the first patient in the randomized portion of Borrower’s Tamibarotene (formerly SY-1425) Phase 2 trial for RARA-positive patients with newly diagnosed unfit acute myeloid leukemia or (ii) enrolled its first patient in

Borrower’s SY-2101 Phase 3 trial for acute promyelocytic leukemia, and (b) Borrower’s written election to pay the Second Interest-Only Extension Milestone Fee either (i) within five (5) Business Days of confirmation from Collateral Agent that the Amortization Date is September 1, 2024 or (ii) upon the earliest to occur of (A) the Maturity Date, (B) the acceleration of any Term Loan, or (C) the prepayment of any Term Loan pursuant to Section 2.2(c) or (d).

“Second Interest-Only Extension Milestone Fee” means a fee, due and payable to Lenders in accordance with their respective Pro Rata Shares if the Amortization Date is September 1, 2024, in the aggregate

amount equal to: (a) if Borrower has elected to pay such fee within five (5) Business Days of confirmation from Collateral Agent that the Amortization Date is September 1, 2024, One Hundred Fifty Thousand Dollars (\$150,000.00), or (b) if Borrower has elected to pay such fee upon the earliest to occur of (A) the Maturity Date, (B) the acceleration of any Term Loan, or (C) the prepayment of any Term Loan pursuant to Section 2.2(c) or (d), Three Hundred Thousand Dollars (\$300,000.00).

4. Limitation of Amendment.

4.1 Except for the consents set forth in Section 2 above, Collateral Agent and the Required Lenders have not consented to, and are not consenting to, any other transaction or action or inaction in violation of the Loan Agreement or any other Loan Document, whether in connection with the Merger or otherwise.

4.2 The consents set forth in Section 2 above and the amendments set forth in Section 3 above are effective for the purposes set forth herein and shall be limited precisely as written and shall not be deemed to (a) be a consent to any amendment, waiver or modification of any other term or condition of any Loan Document, including, without limitation, a waiver of any default or Event of Default under the Loan Agreement resulting from Borrower's failure to consummate the Merger or the breach or fulfillment of any of Borrower's obligations under the Merger Agreement or the Securities Purchase Agreement or (b) otherwise prejudice any right, remedy or obligation which Lenders or Borrower may now have or may have in the future under or in connection with any Loan Document, as amended hereby.

4.3 This Amendment shall be construed in connection with and as part of the Loan Documents and all terms, conditions, representations, warranties, covenants and agreements set forth in the Loan Documents are hereby ratified and confirmed and shall remain in full force and effect.

5. Representations and Warranties. To induce Collateral Agent and the Required Lenders to enter into this Amendment, Borrower hereby represents and warrants to Collateral Agent and the Required Lenders as follows:

5.1 Immediately after giving effect to this Amendment (a) the representations and warranties contained in the Loan Documents are true, accurate and complete in all material respects as of the date hereof (except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date) and (b) no Event of Default has occurred and is continuing;

5.2 Borrower has the power and due authority to execute and deliver this Amendment and to perform its obligations under the Loan Agreement, as amended by this Amendment;

5.3 The organizational documents of Borrower delivered to Collateral Agent on the Effective Date, and updated pursuant to subsequent deliveries by or on behalf of the Borrower to the Collateral Agent, remain true, accurate and complete and have not been amended, supplemented or restated and are and continue to be in full force and effect;

5.4 The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not contravene (i) any material law or regulation binding on or affecting Borrower, (ii) any material contractual restriction with a Person binding on Borrower, (iii) any order, judgment or decree of any court or other governmental or public body or authority, or subdivision thereof, binding on Borrower, or (iv) the organizational documents of Borrower;

5.5 The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not require any order, consent, approval, license, authorization or validation of, or filing, recording or registration with, or exemption by any governmental or public body or authority, or subdivision thereof, binding on Borrower, except as already has been obtained or made;

5.6 This Amendment has been duly executed and delivered by Borrower and is the binding obligation of Borrower, enforceable against Borrower in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, liquidation, moratorium or other similar laws of general application and equitable principles relating to or affecting creditors' rights.

6. Loan Document. Borrower, Lenders and Collateral Agent agree that this Amendment shall be a Loan Document. Except as expressly set forth herein, the Loan Agreement and the other Loan Documents shall continue in full force and effect without alteration or amendment. This Amendment and the Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements.

7. Release by Borrower.

7.1 FOR GOOD AND VALUABLE CONSIDERATION, Borrower hereby forever relieves, releases, and discharges Collateral Agent and each Lender and their respective present or former employees, officers, directors, agents, representatives, attorneys, and each of them, from any and all claims, debts, liabilities, demands, obligations, promises, acts, agreements, costs and expenses, actions and causes of action, of every type, kind, nature, description or character whatsoever, whether known or unknown, suspected or unsuspected, absolute or contingent, arising out of or in any manner whatsoever connected with or related to facts, circumstances, issues, controversies or claims existing or arising from the beginning of time through and including the date of execution of this Amendment solely to the extent such claims arise out of or are in any manner whatsoever connected with or related to the Loan Documents, the Recitals hereto, any instruments, agreements or documents executed in connection with any of the foregoing or the origination, negotiation, administration, servicing and/or enforcement of any of the foregoing (collectively “**Released Claims**”).

7.2 By entering into this release, Borrower recognizes that no facts or representations are ever absolutely certain and it may hereafter discover facts in addition to or different from those which it presently knows or believes to be true, but that it is the intention of Borrower hereby to fully, finally and forever settle and release all matters, disputes and differences, known or unknown, suspected or unsuspected in relation to the Released Claims; accordingly, if Borrower should subsequently discover that any fact that it relied upon in entering into this release was untrue, or that any understanding of the facts was incorrect, Borrower shall not be entitled to set aside this release by reason thereof, regardless of any claim of mistake of fact or law or any other circumstances whatsoever. Borrower acknowledges that it is not relying upon and has not relied upon any representation or statement made by Collateral Agent or Lenders with respect to the facts underlying this release or with regard to any of such party’s rights or asserted rights.

7.3 This release may be pleaded as a full and complete defense and/or as a cross-complaint or counterclaim against any action, suit, or other proceeding that may be instituted, prosecuted or attempted in breach of this release. Borrower acknowledges that the release contained herein constitutes a material inducement to Collateral Agent and the Lenders to enter into this Amendment, and that Collateral Agent and the Lenders would not have done so but for Collateral Agent’s and the Lenders’ expectation that such release is valid and enforceable in all events.

8. Co-Borrower. Within thirty (30) days of the closing of the Merger, Borrower shall cause Tyme Technologies, Inc. to become a co-Borrower and take the actions required by Section 6.12 of the Loan Agreement

9. Effectiveness. This Amendment shall be deemed effective as of the date hereof upon the due execution of (i) this Amendment by the parties thereto, and (ii) a certificate from a Responsible Officer together with Board approved projections certifying and setting forth in reasonable detail that Borrower has enough cash on hand to pay its projected expenses and all debt service when due for a period of eighteen (18) months after the consummation of the Merger and after giving effect to the Merger and other matters related to the Merger set forth therein.

10. Counterparts. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Delivery by electronic transmission (e.g. “.pdf”) of an executed counterpart of this Amendment shall be effective as a manually executed counterpart signature thereof.

11. Governing Law. This Amendment and the rights and obligations of the parties hereto shall be governed by and construed in accordance with the laws of the State of New York.

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IN WITNESS WHEREOF, the parties hereto have caused this First Amendment to Loan and Security Agreement to be executed as of the date first set forth above.

BORROWER:

SYROS PHARMACEUTICALS, INC.

By /s/ Jason Haas

Name: Jason Haas

Title: Chief Financial Officer

COLLATERAL AGENT AND LENDER:

OXFORD FINANCE LLC

By /s/ Colette H. Featherly

Name: Colette H. Featherly

Title: Senior Vice President

[Signature Page to First Amendment to Loan and Security Agreement]

SECOND AMENDMENT TO LOAN AND SECURITY AGREEMENT

THIS SECOND AMENDMENT TO LOAN AND SECURITY AGREEMENT (this “**Amendment**”) is entered into as of August 31, 2022, by and among OXFORD FINANCE LLC, a Delaware limited liability company with an office located at 115 South Union Street, Suite 300, Alexandria, Virginia 22314 (“**Oxford**”), as collateral agent (in such capacity, “**Collateral Agent**”), the Lenders listed on Schedule 1.1 to the Loan Agreement (as defined below) or otherwise a party thereto from time to time including Oxford in its capacity as a Lender (each a “**Lender**” and collectively, the “**Lenders**”), and SYROS PHARMACEUTICALS, INC., a Delaware corporation with offices located at 840 Memorial Drive, Cambridge, MA 02139 (“**Borrower**”).

A. Collateral Agent, Borrower and Lenders have entered into that certain Loan and Security Agreement dated as of February 12, 2020 (as amended, supplemented or otherwise modified from time to time, the “**Loan Agreement**”) pursuant to which Lenders have provided to Borrower certain loans in accordance with the terms and conditions thereof;

B. Borrower has requested that Collateral Agent and the Required Lenders modify certain provisions of the Loan Agreement; and

C. Collateral Agent and the Required Lenders have agreed to amend certain provisions of the Loan Agreement, subject to, and in accordance with, the terms and conditions set forth herein, and in reliance upon the representations and warranties set forth herein.

Agreement

NOW, THEREFORE, in consideration of the promises, covenants and agreements contained herein, and other good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, Borrower, the Required Lenders and Collateral Agent hereby agree as follows:

1. Definitions. Capitalized terms used but not defined in this Amendment shall have the meanings given to them in the Loan Agreement.

2. Amendments to Loan Agreement.

2.1 Section 6.10 (Financial Covenant). Section 6.10 of the Loan Agreement is amended and restated as follows:

“**6.10 MSC Investment Condition.** Borrower shall maintain unrestricted cash balance in one or more Control Accounts subject to Control Agreements in favor of Collateral Agent in an aggregate amount of not less than an amount equal to the lesser of (i) One Hundred Ten percent (110.00%) of the aggregate principal amount of outstanding Obligations (provided, however, for the period from August 1, 2022 through September 23, 2022 only, such percent during such period shall be Ninety percent (90.00%) of the aggregate principal amount of outstanding Obligations) and (ii) the amount of Borrower’s and all of its Subsidiaries’ (including Syros Securities) aggregate consolidated cash and Cash Equivalent assets (the “**MSC Investment Condition**”).”

2.2 Compliance Certificate (Exhibit C). Exhibit C to the Loan Agreement is amended by replacing the summary of the MSC Investment Condition with the following:

“Not less than the lesser of (i) One Hundred Ten percent (110.00%) of the aggregate principal amount of outstanding Term Loans (provided, however, for the period from August 1, 2022 through September 23, 2022 only, such percent during such period shall be Ninety percent (90.00%) of the aggregate principal amount of outstanding Term Loans) and (ii) the amount of Borrower’s and all of its Subsidiaries’ aggregate consolidated cash and Cash Equivalent assets”.

3.Limitation of Amendment.

3.1 The amendments set forth in Section 2 above are effective for the purposes set forth herein and shall be limited precisely as written and shall not be deemed to (a) be a consent to any amendment, waiver or modification of any other term or condition of any Loan Document or (b) otherwise prejudice any right, remedy or obligation which Lenders or Borrower may now have or may have in the future under or in connection with any Loan Document, as amended hereby.

3.2 This Amendment shall be construed in connection with and as part of the Loan Documents and all terms, conditions, representations, warranties, covenants and agreements set forth in the Loan Documents are hereby ratified and confirmed and shall remain in full force and effect.

4.Representations and Warranties. To induce Collateral Agent and the Required Lenders to enter into this Amendment, Borrower hereby represents and warrants to Collateral Agent and the Required Lenders as follows:

4.1 Immediately after giving effect to this Amendment (a) the representations and warranties contained in the Loan Documents are true, accurate and complete in all material respects as of the date hereof (except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date) and (b) no Event of Default has occurred and is continuing;

4.2 Borrower has the power and due authority to execute and deliver this Amendment and to perform its obligations under the Loan Agreement, as amended by this Amendment;

4.3 The organizational documents of Borrower delivered to Collateral Agent on the Effective Date, and updated pursuant to subsequent deliveries by or on behalf of the Borrower to the Collateral Agent, remain true, accurate and complete and have not been amended, supplemented or restated and are and continue to be in full force and effect;

4.4 The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not contravene (i) any material law or regulation binding on or affecting Borrower, (ii) any material contractual restriction with a Person binding on Borrower, (iii) any order, judgment or decree of any court or other governmental or public body or authority, or subdivision thereof, binding on Borrower, or (iv) the organizational documents of Borrower;

4.5 The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not require any order, consent, approval, license, authorization or validation of, or filing, recording or registration with, or exemption by any governmental or public body or authority, or subdivision thereof, binding on Borrower, except as already has been obtained or made;

4.6 This Amendment has been duly executed and delivered by Borrower and is the binding obligation of Borrower, enforceable against Borrower in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, liquidation, moratorium or other similar laws of general application and equitable principles relating to or affecting creditors' rights.

5.Loan Document. Borrower, Lenders and Collateral Agent agree that this Amendment shall be a Loan Document. Except as expressly set forth herein, the Loan Agreement and the other Loan Documents shall continue in full force and effect without alteration or amendment. This Amendment and the Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements.

6.Release by Borrower.

6.1 FOR GOOD AND VALUABLE CONSIDERATION, Borrower hereby forever relieves, releases, and discharges Collateral Agent and each Lender and their respective present or former employees, officers, directors, agents, representatives, attorneys, and each of them, from any and all claims, debts, liabilities, demands, obligations, promises, acts, agreements, costs and expenses, actions and causes of action, of every type, kind, nature, description or character whatsoever, whether known or unknown, suspected or unsuspected, absolute or contingent, arising out of or in any manner whatsoever connected with or related to facts, circumstances, issues, controversies or claims existing

or arising from the beginning of time through and including the date of execution of this Amendment solely to the extent such claims arise out of or are in any manner whatsoever connected with or related to the Loan Documents, the Recitals hereto, any instruments, agreements or documents executed in connection with any of the foregoing or the origination, negotiation, administration, servicing and/or enforcement of any of the foregoing (collectively "**Released Claims**").

6.2 By entering into this release, Borrower recognizes that no facts or representations are ever absolutely certain and it may hereafter discover facts in addition to or different from those which it presently knows or believes to be true, but that it is the intention of Borrower hereby to fully, finally and forever settle and release all matters, disputes and differences, known or unknown, suspected or unsuspected in relation to the Released Claims; accordingly, if Borrower should subsequently discover that any fact that it relied upon in entering into this release was untrue, or that any understanding of the facts was incorrect, Borrower shall not be entitled to set aside this release by reason thereof, regardless of any claim of mistake of fact or law or any other circumstances whatsoever. Borrower acknowledges that it is not relying upon and has not relied upon any representation or statement made by Collateral Agent or Lenders with respect to the facts underlying this release or with regard to any of such party's rights or asserted rights.

6.3 This release may be pleaded as a full and complete defense and/or as a cross-complaint or counterclaim against any action, suit, or other proceeding that may be instituted, prosecuted or attempted in breach of this release. Borrower acknowledges that the release contained herein constitutes a material inducement to Collateral Agent and the Lenders to enter into this Amendment, and that Collateral Agent and the Lenders would not have done so but for Collateral Agent's and the Lenders' expectation that such release is valid and enforceable in all events.

7.Effectiveness. This Amendment shall be deemed effective as of the date hereof upon the due execution of this Amendment by the parties thereto.

8.Counterparts. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Delivery by electronic transmission (e.g. ".pdf") of an executed counterpart of this Amendment shall be effective as a manually executed counterpart signature thereof.

9.Governing Law. This Amendment and the rights and obligations of the parties hereto shall be governed by and construed in accordance with the laws of the State of New York.

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IN WITNESS WHEREOF, the parties hereto have caused this Second Amendment to Loan and Security Agreement to be executed as of the date first set forth above.

BORROWER:

SYROS PHARMACEUTICALS, INC.

By /s/ Jason Haas

Name: Jason Haas

Title: Chief Financial Officer

COLLATERAL AGENT AND LENDER:

OXFORD FINANCE LLC

By /s/ Colette H. Featherly

Name: Colette H. Featherly

Title: Senior Vice President

[Signature Page to Second Amendment to Loan and Security Agreement]

THIRD AMENDMENT TO LOAN AND SECURITY AGREEMENT

THIS THIRD AMENDMENT TO LOAN AND SECURITY AGREEMENT (this “**Amendment**”) is entered into as of November 15, 2022, by and among **OXFORD FINANCE LLC**, a Delaware limited liability company with an office located at 115 South Union Street, Suite 300, Alexandria, Virginia 22314 (“**Oxford**”), as collateral agent (in such capacity, “**Collateral Agent**”), the Lenders listed on Schedule 1.1 to the Loan Agreement (as defined below) or otherwise a party thereto from time to time including Oxford in its capacity as a Lender (each a “**Lender**” and collectively, the “**Lenders**”), **SYROS PHARMACEUTICALS, INC.**, a Delaware corporation with offices located at 35 CambridgePark Drive, Cambridge, MA 02140 (“**Existing Borrower**”), **TYME TECHNOLOGIES, INC.**, a Delaware corporation with offices located at 35 CambridgePark Drive, Cambridge, MA 02140 (“**Tyme Parent**”) and **TYME INC.**, a Delaware corporation with offices located at 35 CambridgePark Drive, Cambridge, MA 02140 (“**Tyme Sub**” and together with Tyme Parent, each a “**New Borrower**” and collectively, “**New Borrowers**”; and together with Existing Borrower, individually and collectively, jointly and severally, “**Borrower**”).

Recitals

- a) Collateral Agent, Existing Borrower and Lenders have entered into that certain Loan and Security Agreement dated as of February 12, 2020, as amended by that certain First Amendment to Loan and Security Agreement dated as of July 3, 2022, and as amended by that certain Second Amendment to Loan and Security Agreement dated as of August 31, 2022 (as amended, supplemented or otherwise modified from time to time, the “**Loan Agreement**”) pursuant to which Lender have provided to Existing Borrower certain loans in accordance with the terms and conditions thereof.
- b) Existing Borrower has acquired Tyme Parent, and Tyme Parent has become a wholly owned subsidiary of Existing Borrower, pursuant to the terms of that certain Agreement and Plan of Merger dated as of July 3, 2022 by and among Existing Borrower, Tack Acquisition Corp., a Delaware corporation, and New Borrower, and Tyme Sub is a wholly owned subsidiary of Tyme Parent.
- c) Each New Borrower is required to become a Borrower under the Loan Agreement.
- d) Collateral Agent and the Required Lenders have agreed to amend certain provisions of the Loan Agreement, subject to, and in accordance with, the terms and conditions set forth herein, and in reliance upon the representations and warranties set forth herein.

Agreement

NOW, THEREFORE, in consideration of the promises, covenants and agreements contained herein, and other good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, Borrower, the Required Lenders and Collateral Agent hereby agree as follows:

1. Definitions. Capitalized terms used but not defined in this Amendment shall have the meanings given to them in the Loan Agreement.

2. Joinder.

2.1. New Borrowers. Each New Borrower is hereby each added as a “Borrower” under the Loan Agreement. All references in the Loan Agreement to “Borrower” shall hereafter mean and include the Existing Borrower and New Borrowers individually and collectively, jointly and severally; and New Borrowers shall hereafter have all rights, duties and obligations of “Borrower” thereunder.

2.2. Joinder to Loan Agreement. Each New Borrower hereby joins the Loan Agreement and each of the Loan Documents (other than the Warrants) and agrees to comply with and be bound by all of the terms, conditions and covenants of the Loan Agreement and Loan Documents (other than the Warrants), as if it were originally named a “Borrower” therein. Without limiting the generality of the preceding sentence, each New Borrower agrees that it will be jointly and severally liable, together with Existing Borrower, for the payment and performance of all obligations and liabilities of Borrower under the Loan Agreement, including, without limitation, the Obligations. Each Borrower hereby appoints the other as agent for the other for all purposes hereunder. Each Borrower hereunder shall be obligated to repay all Credit Extensions made pursuant to the Loan Agreement, regardless of which Borrower actually receives said Credit Extension, as if each Borrower hereunder directly received all Credit Extensions.

2.3. Subrogation and Similar Rights. Each Borrower waives (a) any suretyship defenses available to it under the Code or any other applicable law, and (b) any right to require Collateral Agent or any

Lender to: (i) proceed against any Borrower or any other person; (ii) proceed against or exhaust any security; or (iii) pursue any other remedy. Collateral Agent and any Lender may exercise or not exercise any right or remedy it has against any Borrower or any security it holds (including the right to foreclose by judicial or non-judicial sale) without affecting any Borrower's liability. Notwithstanding any other provision of this Amendment, the Loan Agreement, the Loan Documents or any other related documents, each Borrower irrevocably waives all rights that it may have at law or in equity (including, without limitation, any law subrogating Borrower to the rights of Collateral Agent and the Lenders under this Amendment and the Loan Agreement) to seek contribution, indemnification or any other form of reimbursement from any other Borrower, or any other Person now or hereafter primarily or secondarily liable for any of the Obligations, for any payment made by Borrower with respect to the Obligations in connection with this Amendment, the Loan Agreement or otherwise and all rights that it might have to benefit from, or to participate in, any security for the Obligations as a result of any payment made by Borrower with respect to the Obligations in connection with this Amendment, the Loan Agreement or otherwise. Any agreement providing for indemnification, reimbursement or any other arrangement prohibited under this Section shall be null and void. If any payment is made to a Borrower in contravention of this Section, such Borrower shall hold such payment in trust for Collateral Agent and the Lenders and such payment shall be promptly delivered to Collateral Agent for application to the Obligations, whether matured or unmatured.

2.4. Grant of Security Interest. Each New Borrower hereby grants Collateral Agent, for the ratable benefit of the Lenders, to secure the payment and performance in full of all of the Obligations, a continuing security interest in, and pledges to Collateral Agent, for the ratable benefit of the Lenders, the Collateral, wherever located, whether now owned or hereafter acquired or arising, and all proceeds and products thereof. Each New Borrower represents, warrants, and covenants that the security interest granted herein is and shall at all times continue to be a first priority perfected security interest in the Collateral, subject only to Permitted Liens that are permitted by the terms of the Loan Agreement to have priority to Collateral Agent's Lien. Each New Borrower hereby authorizes Collateral Agent to file financing statements or take any other action required to perfect Collateral Agent's security interests in the Collateral, without notice to Borrower, with all appropriate jurisdictions to perfect or protect Collateral Agent's interest or rights under the Loan Documents, including a notice that any disposition of the Collateral, except to the extent permitted by the terms of the Loan Agreement, by each New Borrower, or any other Person, shall be deemed to violate the rights of Collateral Agent under the Code.

2.5. Representations and Warranties. Each New Borrower hereby represents and warrants to Collateral Agent and each Lender that all representations and warranties in the Loan Documents made on the part of Existing Borrower are true and correct in all material respects on the date hereof (except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date) with respect to Existing Borrower and each New Borrower, with the same force and effect as if each New Borrower were named as "Borrower" in the Loan Documents in addition to Existing Borrower.

3. Amendments to Loan Agreement.

3.1. General. Each reference to the phrase "[n]either Borrower" in the Loan Agreement hereby is replaced with "[n]o Borrower."

3.2. Section 13 (Definitions). The following defined term in Section 13 of the Loan Agreement is amended and restated as follows:

"**Basic Rate**" is, with respect to each Term Loan, the floating per annum rate of interest (based on a year of three hundred sixty (360) days) equal to the greater of (i) seven and seventy-five hundredths of one percent (7.75%) and (ii) the sum of (a) 1-Month CME Term SOFR on the last Business Day of the month that immediately precedes the month in which the interest will accrue, (b) one-tenth of one percent (0.10%), and (c) five and ninety-eight hundredths of one percent (5.98%). Notwithstanding the foregoing, (i) in no event shall the Basic Rate for any Term Loan be less than seven and seventy-five hundredths of one percent (7.75%) and (ii) upon the occurrence of a Benchmark Transition Event, Collateral Agent may, in good faith and with reference to the margin above such interest rate in this definition, amend this Agreement to replace the Benchmark

with a replacement interest rate and replacement margin above such interest rate that results in a substantially similar interest rate floor and a total rate in effect immediately prior to the effectiveness of such replacement interest rate and replacement margin, and any such amendment shall become effective at 5:00 p.m. Eastern time on the third Business Day after Collateral Agent has notified Borrower of such amendment. Any determination, decision or election that may be made by Collateral Agent pursuant hereto will be conclusive and binding absent manifest error and may be made in Collateral Agent's sole discretion and without consent from any other party.

3.3.Section 13 (Definitions). The following defined terms are added to Section 13 of the Loan Agreement as follows:

"1-Month CME Term SOFR" is the 1-month CME Term SOFR reference rate as published by the CME Term SOFR Administrator on the CME Term SOFR Administrator's Website.

"Benchmark" is, initially, the 1-Month CME Term SOFR; provided, that if a Benchmark Transition Event has occurred with respect to the 1-Month CME Term SOFR or the then-current Benchmark, then "Benchmark" means the applicable replacement rate that has replaced the immediately preceding benchmark rate pursuant to the defined term "Basic Rate".

"Benchmark Transition Event" means the occurrence of one or more of the following events with respect to the then-current Benchmark:

- (a) a public statement or publication of information by or on behalf of the administrator for such Benchmark announcing that such Person has ceased or will cease to provide such Benchmark, permanently or indefinitely, provided that, at the time of such statement or publication, there is no successor administrator that will continue to provide such Benchmark;
- (b) a public statement or publication of information by the regulatory supervisor for the administrator for such Benchmark, the U.S. Federal Reserve System, an insolvency official with jurisdiction over the administrator for such Benchmark, a resolution authority with jurisdiction over the administrator for such Benchmark or a court or an entity with similar insolvency or resolution authority over the administrator for such Benchmark, which states that the administrator for such Benchmark has ceased or will cease to provide such Benchmark permanently or indefinitely, provided that, at the time of such statement or publication, there is no successor administrator that will continue to provide such Benchmark; or
- (c) a public statement or publication of information by the regulatory supervisor for the administrator for such Benchmark announcing that such Benchmark is no longer representative or in compliance with the International Organization of Securities Commissions Principles for Financial Benchmarks.

"CME Term SOFR Administrator" is CME Group Benchmark Administration Limited, as administrator of the forward-looking term SOFR, or any successor administrator.

"CME Term SOFR Administrator's Website" is the website of the CME Group Benchmark Administrator at <http://www.cmegroup.com>, or any successor source.

4.Limitation of Joinder and Amendment.

4.1. The joinder and amendment set forth in **Sections 2 and 3** are effective for the purposes set forth herein and shall be limited precisely as written and shall not be deemed to (a) be a consent to any amendment, waiver or modification of any other term or condition of any Loan Document, or (b) otherwise prejudice any right, remedy or obligation which Collateral Agent, any Lender or Borrower may now have or may have in the future under or in connection with any Loan Document, as amended hereby.

4.2. This Amendment shall be construed in connection with and as part of the Loan Documents and all terms, conditions, representations, warranties, covenants and agreements set forth in the Loan Documents, are hereby ratified and confirmed and shall remain in full force and effect.

5.Representations and Warranties. To induce Collateral Agent and the Required Lenders to enter into this Amendment, Existing Borrower hereby represents and warrants to Collateral Agent and the Required Lenders as follows:

5.1.Immediately after giving effect to this Amendment (a) the representations and warranties contained in the Loan Documents are true, accurate and complete in all material respects as of the date hereof (except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date) and (b) no Event of Default has occurred and is continuing;

5.2.Existing Borrower has the power and due authority to execute and deliver this Amendment and to perform its obligations under the Loan Agreement, as amended by this Amendment;

5.3.The organizational documents of Existing Borrower delivered to Collateral Agent and Lenders on the Effective Date, and updated pursuant to subsequent deliveries by or on behalf of the Existing Borrower to the Collateral Agent remain true, accurate and complete and have not been amended, supplemented or restated and are and continue to be in full force and effect;

5.4.The execution and delivery by Existing Borrower of this Amendment and the performance by Existing Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not contravene (i) any material law or regulation binding on or affecting Existing Borrower, (ii) any material contractual restriction with a Person binding on Existing Borrower, (iii) any order, judgment or decree of any court or other governmental or public body or authority, or subdivision thereof, binding on Existing Borrower, or (iv) the organizational documents of Existing Borrower;

5.5.The execution and delivery by Existing Borrower of this Amendment and the performance by Existing Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not require any order, consent, approval, license, authorization or validation of, or filing, recording or registration with, or exemption by any governmental or public body or authority, or subdivision thereof, binding on Existing Borrower, except as already has been obtained or made; and

5.6.This Amendment has been duly executed and delivered by Borrower and is the binding obligation of Borrower, enforceable against Borrower in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, liquidation, moratorium or other similar laws of general application and equitable principles relating to or affecting creditors' rights.

6.Loan Document. Borrower, Lenders and Collateral Agent agree that this Amendment shall be a Loan Document. Except as expressly set forth herein, the Loan Agreement and the other Loan Documents shall continue in full force and effect without alteration or amendment. This Amendment and the Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements.

7.Effectiveness. This Amendment shall be deemed effective as of the date hereof upon the due execution and delivery to Collateral Agent and Lenders of the following:

7.1.1.this Amendment duly executed by each party hereto;

7.1.2.an Officer's Certificate duly executed by each New Borrower, relating to the Operating Documents, corporate authorizations and other matters in a form reasonably acceptable to Collateral Agent and the Lenders;

7.1.3.completed Perfection Certificates duly executed by each New Borrower and Existing Borrower;

7.1.4.Amended and Restated Secured Promissory Notes duly executed by each Borrower;

7.1.5.good standing certificates for each New Borrower certified by the Secretary of State (or equivalent agency) of the State of Delaware and each jurisdiction in which each New Borrower is qualified to conduct business, each as of a date no earlier than thirty (30) days prior to the date of this Amendment;

7.1.6.a duly filed UCC Financing Statement with the Secretary of State of the State of Delaware, identifying New Borrower as a debtor;

7.1.7.to the extent such Shares are certificated, the certificates for the Shares of each New Borrower, together with Assignment(s) Separate from Certificate, duly executed in blank;

7.1.8.updated insurance certificates including each New Borrower as an insured; and

7.1.9.duly-executed Control Agreements in favor of Collateral Agent for all Collateral Accounts of each New Borrower required by Section 6.6 of the Loan Agreement, except a Control Agreement shall not be required for the Collateral Account at Oppenheimer ending in -1765 (the “**Oppenheimer Account**”) so long as by no later than November 30, 2022, Collateral Agent shall have received, in form and substance reasonably satisfactory to Collateral Agent, evidence that the Oppenheimer Account has been closed.

8.Conditions Subsequent. No later than thirty (30) days after the date of this Amendment (or such longer period as Collateral Agent shall agree in its sole discretion) Borrower agrees to provide duly-executed landlord consents and/or bailee waivers for each New Borrower’s (a) leased real property and/or (b) bailee location, in each case to the extent required by Section 6.11 of the Loan Agreement.

9.Counterparts. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Delivery by electronic transmission (e.g. “.pdf”) of an executed counterpart of this Amendment shall be effective as a manually executed counterpart signature thereof.

10.Governing Law. This Amendment and the rights and obligations of the parties hereto shall be governed by and construed in accordance with the laws of the State of New York.

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In Witness Whereof, the parties hereto have caused this Amendment to be duly executed and delivered as of the date first written above.

COLLATERAL AGENT AND LENDER:

OXFORD FINANCE LLC

By: /s/ Collette H. Featherly

Name: Collette H. Featherly

Title: Senior Vice President

BORROWER:

SYROS PHARMACEUTICALS, INC.

By: /s/ Jason Haas

Name: Jason Haas

Title: Chief Financial Officer

TYME TECHNOLOGIES, INC.

By: /s/ Jason Haas

Name: Jason Haas

Title: Treasurer and Secretary

TYME INC.

By: /s/ Jason Haas

Name: Jason Haas

Title: Trasurer

[Signature Page to Third Amendment to Loan and Security Agreement]

Subsidiaries of the Registrant

| <u>Name of Entity</u> | <u>Jurisdiction of Incorporation</u> | <u>Percent Owned by the Registrant</u> |
|---|--------------------------------------|--|
| Syros Securities Corporation | Massachusetts | 100% |
| Syros Pharmaceuticals (Ireland) Limited | Ireland | 100% |
| Tyme Technologies, Inc. | Delaware | 100% |
| Tyme, Inc. | Delaware | 100% |

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

- 1.Registration Statement (Form S-8 No. 333-212363) pertaining to the 2012 Equity Incentive Plan, 2016 Stock Incentive Plan, and 2016 Employee Stock Purchase Plan of Syros Pharmaceuticals, Inc.,
- 2.Registration Statements (Form S-8 Nos. 333-216821, 333-223574, 333-230116, 333-236895 and 333-253861) pertaining to the 2016 Stock Incentive Plan and 2016 Employee Stock Purchase Plan of Syros Pharmaceuticals, Inc.,
- 3.Registration Statement (Form S-8 No. 333-263555) pertaining to the 2016 Stock Incentive Plan, 2016 Employee Stock Purchase Plan, 2022 Inducement Stock Incentive Plan, and Nonstatutory Stock Option Agreements for Inducement Awards of Syros Pharmaceuticals, Inc.,
- 4.Registration Statement (Form S-8 No. 333-267451) pertaining to the 2016 Stock Incentive Plan of Syros Pharmaceuticals, Inc.,
- 5.Registration Statement (Form S-3 No. 333-222634) of Syros Pharmaceuticals, Inc.,
- 6.Registration Statement (Form S-3 No. 333-239141) of Syros Pharmaceuticals, Inc.,
- 7.Registration Statement (Form S-3 No. 333-251941) of Syros Pharmaceuticals, Inc., and
- 8.Registration Statement (Form S-3 No. 333-267888) of Syros Pharmaceuticals, Inc.

of our report dated March 2, 2023, with respect to the consolidated financial statements of Syros Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2022.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 2, 2023

**Certification of Principal Executive Officer pursuant to Exchange Act Rules 13a-14(a)
and 15d-14(a), as adopted pursuant to Section 302 of Sarbanes-Oxley Act of 2002**

I, Nancy Simonian, certify that:

1. I have reviewed this Annual Report on Form 10-K of Syros Pharmaceuticals, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Syros Pharmaceuticals, Inc.

/s/ Nancy Simonian, M.D.

Nancy Simonian, M.D.

President and Chief Executive Officer

(Principal Executive Officer)

Dated: March 2, 2023

**Certification of Principal Financial Officer pursuant to Exchange Act Rules 13a-14(a)
and 15d-14(a), as adopted pursuant to Section 302 of Sarbanes-Oxley Act of 2002**

I, Jason Haas, certify that:

1. I have reviewed this Annual Report on Form 10-K of Syros Pharmaceuticals, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Syros Pharmaceuticals, Inc.

/s/ Jason Haas

Jason Haas

Chief Financial Officer
(Principal Financial Officer)

Dated: March 2, 2023

**CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT
TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report on Form 10-K of Syros Pharmaceuticals, Inc. (the “Company”) for the fiscal year ended December 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the “Report”), the undersigned, Nancy Simonian, President and Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of her knowledge:

- (1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 2, 2023

/s/ Nancy Simonian, M.D.
Nancy Simonian, M.D.
President and Chief Executive Officer
(Principal Executive Officer)

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

**CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT
TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report on Form 10-K of Syros Pharmaceuticals, Inc. (the “Company”) for the fiscal year ended December 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the “Report”), the undersigned, Jason Haas, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of his knowledge:

- (1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 2, 2023

/s/ Jason Haas
Jason Haas
Chief Financial Officer
(Principal Financial Officer)

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.
