UNITED STATES SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT Pursuant to Section 13 or 15(d) of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 15, 2018

Syros Pharmaceuticals, Inc.

(Exact Name of Registrant as Specified in its Charter)

001-37813

(Commission

Delaware (State or Other Jurisdiction of Incorporation)

File Number)

620 Memorial Drive, Suite 300 Cambridge, Massachusetts (Address of Principal Executive Offices) 45-3772460 (IRS Employer Identification No.)

02139 (Zip Code)

Registrant's telephone number, including area code: (617) 744-1340

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company \square

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.

Item 7.01 Regulation FD Disclosure

On November 15, 2018, Syros Pharmaceuticals, Inc. (the "**Company**") held a conference call and webcast in which the Company's management reviewed a slide presentation describing, among other things, data from the dose-escalation portion of the Company's Phase 1 clinical trial of SY-1365. This slide presentation is attached as Exhibit 99.1 to this Form 8-K and incorporated herein by reference.

The information responsive to Item 7.01 of this Form 8-K and Exhibit 99.1 hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "**Exchange Act**") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On November 15, 2018, the Company issued a press release reporting data from the dose-escalation portion of its Phase 1 clinical trial of SY-1365. A copy of this press release is filed as Exhibit 99.2 to this Form 8-K and incorporated herein by reference. The information contained on websites referenced in this press release is not incorporated herein.

Item 9.01 Financial Statements and Exhibits.

Exhibit No.		Description	
99.1	Slide presentation dated November 15, 2018		
99.2	Press release dated November 15, 2018		
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SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

SYROS PHARMACEUTICALS, INC.

Date: November 15, 2018

By: /s/ Gerald E. Quirk Gerald E. Quirk Chief Legal & Administrative Officer



Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding the potential benefits of CDK7 inhibition and of SY-1365 and statements regarding our strategy, research and clinical development plans, collaborations, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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 these forward-looking statements as a result of various important factors, including Syros' ability to: advance the development of its programs, including SY-1365, under the timelines it projects in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; replicate scientific and non-clinical data in clinical trials; obtain and maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; obtain and maintain necessary regulatory approvals; identify, enter into and maintain collaboration agreements with third parties; manage competition; manage expenses; raise the substantial additional capital needed to achieve its business objectives; attract and retain qualified personnel; and successfully execute on its business strategies; risks described under the caption "Risk Factors" in Syros' Annual Report on Form 10-K for the year ended December 31, 2017, as updated in its Quarterly Reports on Form 10-Q for the quarters ended March 31, June 30 and September 30, 2018, each of which is on file with the future.

Any forward-looking statements contained in this presentation speak only as of the date this presentation is made, and we expressly disclaim any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

SY-1365 (CDK7 inhibitor): Controlling expression of tumor-driving genes

Difficult-to-treat solid tumors and blood cancers



- · First-in-class selective inhibitor of CDK7
- CDK7 inhibition induces apoptosis and preferentially kills cancer cells over non-cancerous cells
- Currently in Phase 1 clinical trial as single and combination agent in ovarian and breast cancers
 - Opened expansion cohorts in September 2018
 - Data from dose escalation phase presented today in oral presentation at EORTC-NCI-AACR 2018 meeting
- Broad potential to expand into additional solid tumors and blood cancers

CDK7 has emerged as a potentially important target across a range of solid tumors and blood cancers



SY-1365 is a first-in-class potent and selective CDK7 inhibitor

- Covalent
- · Highly potent
- · Highly selective
 - Only binds to 7 out of 468 kinases screened at >90% binding
 - Does not significantly bind to CDK9 or cell cycle CDKs
- Preclinical models demonstrated sustained CDK7 occupancy levels >50% maximized antitumor effects, and supported intermittent dosing
- · Durable tumor responses in in vivo models





SY-1365 has dual effect on transcription and cell cycle, preferentially killing cancer cells in preclinical studies



Expansion cohorts in Phase 1 trial exploring SY-1365 as single agent and in combination in multiple ovarian and breast cancer patient populations

Phase 1 clinical trial design					
Dose escalation Status: Completed, data at EORTC-NCI-AACR	Expansion Status: Ongoing				
 Enrolled patients with advanced solid tumors of any histology Explored once- and twice-a-week dosing Primary objective to establish MTD and optimal dose and regimen Assessed safety, PK/PD, proof-of-mechanism 	Relapsed ovarian cancer, 3+ prior lines Single agent (N=24)				
	Relapsed ovarian cancer, 1+ prior lines (platinum sensitive) Combination with carboplatin (N=24)				
	Primary platinum refractory ovarian cancer Single agent pilot (N=12)				
	HR+ metastatic breast cancer, CDK4/6 inhibitor resistant Combination with fulvestrant (N=12)				
	Solid tumors accessible for biopsy Single agent (N=10)				

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Dose escalation portion of SY-1365 Phase 1 trial

Dosing

- IV dosing over one hour
 - 3 weeks every 4 weeks

Trial Endpoints

- Primary: DLTs and safety
- · Secondary: PK and PD
- Exploratory: Anti-tumor activity

Data snapshot: Oct. 15, 2018



SY-1365 dose escalation: patient baseline characteristics

Characteristics N(%)	N=32				
Median Age, years (range)	63 (25-87)				
Female sex, n (%)	25 (78.1)				
≥4 Prior Lines of Therapy	28 (87.5)				
Median Number Prior Lines (range)	5 (1-13)				
Cancer Type					
Breast	8 (25)				
Ovarian	8 (25)				
Endometrial	5 (16)				
Pancreatic	2 (6)				
Other	9 (28)				

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SY-1365 dose escalation: patient disposition

Dose (mg/m²)	2	4	8	16	32	53	64	80	107	112	Total	
Safety Population	1	2	1	1	1	6	7	6	6	1	32	
Response Evaluable	1	1	1	1	1	3	5	3	3	0	19	
Number of Patients Enrolled					N (%)							
Duration of Treatment: Median days (range)							46.5 (2 – 147)					
Patients withdrawn from treatment 28 (87.5)												
Progressive Disease per RECIST 1.1							16 (50.0)					
Clinical Progression						7 (21.9)						
Withdrawal of Consent						4 (12.5)						
Death*						1 (3.1)						
*Due to progression of disease												
YR\S												

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SY-1365 safety overview: dose escalation (N=32)

- · Predominantly low grade, reversible, and generally manageable
- · Most frequent related AEs include headache, nausea, vomiting, and fatigue
- · No reports of neutropenia
- DLTs: headache (64 mg/m²), coronary vasospasm (80 mg/m²), and fatigue (112 mg/m²)
- MTD not defined

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SY-1365 plasma pharmacokinetics



- Plasma PK exposures
 (Cmax, AUC) are linear from doses of 2 to 107 mg/m²
- No SY-1365 accumulation with repeat dosing
- SY-1365 day 1 PK parameters at 80 mg/m²
 - Cmax: 7,498 ± 1,116 ng/mL
 - AUC: 11,696 ± 2,848 ng/mL•h
 - Half-life: 17.9 ± 4.2 h

SY-1365 PD effects evaluated by CDK7 occupancy and transcriptional assays



CDK7 Occupancy: relative measure of free CDK7 to total CDK7

- Transcriptional assay: gene expression signature
 - SY-1365 dose-response gene signature developed in PBMCs in vitro
 - ~25 early response genes (3-5 hrs post treatment)
 - Custom Nanostring codeset to evaluate a subset of response and control genes in patient PBMCs

SY-1365 demonstrates dose-dependent effects on CDK7 occupancy and gene transcription



- SY-1365 binding to CDK7 over the dosing interval exceeded target levels from preclinical efficacy models at doses ≥ 32 mg/m² with plateauing at 80 mg/m² and above
- Similar %CDK7 occupancies observed between PBMCs and xenograft tissues in syngeneic mouse studies, and between PBMCs and tumor biopsies collected from patients (n=2)
- · Transcriptional assay demonstrated SY-1365 dose response relationship with gene expression changes

Early evidence of SY-1365 clinical activity

- Clinical activity per RECIST 1.1 criteria was observed in 7 out of 19 evaluable patients
 Disease Control Rate (CR+PR+SD) of 37%
- One confirmed PR (in clear cell ovarian cancer patient) observed at 80 mg/m² BIW
- 6 additional patients with stable disease, mostly at higher doses (≥ 32 mg/m² BIW)
 - Consists of 2 ovarian, 2 breast and 2 endometrial cancer patients
 - Duration of treatment for these patients ranged from 50 127 days

Early evidence of SY-1365 clinical activity

CT images of 52 year old woman with relapsed ovarian cancer on SY-1365 80 mg/m² BIW



- Stage IV clear cell in 4th relapse
 - ARID1A, PIK3CA, NF1 mutations
- Best response to prior lines of therapy: SD
- Confirmed PR after 2 cycles
 - 31.8% reduction (C3D1)
- Remains on study in PR in 7th month of SY-1365 treatment
 - 49% decrease at C7D1

Dose and schedule selected for ongoing expansion cohorts

- Evaluating SY-1365 as single agent and in combination in multiple ovarian and breast cancer patient populations
- Dose selection supported by PK/PD analyses of drug exposure and target occupancy, tolerability profile and early signs of clinical activity
 - Single agent: 80 mg/m² twice weekly
 - Combination: 80 mg/m² once weekly

SY-1365 Phase 1 Expansion Cohorts

Relapsed ovarian cancer, 3+ prior lines Single agent (N=24)

Relapsed ovarian cancer, 1+ prior lines (platinum sensitive) Combination with carboplatin (N=24)

Primary platinum refractory ovarian cancer Single agent pilot (N=12)

HR+ metastatic breast cancer, CDK4/6 inhibitor resistant Combination with fulvestrant (N=12)

Solid tumors accessible for biopsy Single agent (N=10)

Significant need for new therapies in advanced high-grade serous ovarian and HR+ metastatic breast cancer

Ovarian Cancer : ~59,000 ¹	Breast Cancer : ~266,000 ²
 70% have high-grade serous ovarian car 	• ~80% are HR+ breast cancer
nd most present with advanced sease at initial diagnosis	 Standard-of-care for metastatic HR+ breast cancer includes CDK4/6 inhibitor plus an
 Standard-of-care includes platinum-base 	d aromatase inhibitor
chemotherapy as foundation	 ~50% of patients progress within ~2 years
 Majority of patients, even those who initially respond to platinum-based chemotherapy, r within a year 	 Second-line hormone-based therapies have limited efficacy, creating a need for new therapies
 Significant unmet need and/or limited treatment options in platinum sensitive, resistant and refractory patients 	ulerapies

¹Annual ovarian cancer diagnoses in the U.S., Canada, Japan and the EU 5 (UK, Germany, France, Spain and Italy). Health Advances analysis. ²American Cancer Society estimate of new cases diagnosed in U.S. in 2018

Sources: Hanker et al. Ann Oncol. 2012 Oct;23(10):2605-12. SEER, Cancer Research UK 2013. NCCN Guidelines Nov. 2017. McGluggage WG. Pathology 2011; 43: 420–432. Gabra H. EJC Suppl. 2014 Dec;12(2):2-6. and Herzog TJ and Monk BJ. Onitio AA et al., Clin Med Res 2009; 7(1-2):4-13. Rugo HS et al., JCO 2016; 34: 3069-3103. Finn RS et al. N Engl J Med 2016; 375(20): 1925-1936. Fasiodex USPI











Syros Announces Dose Escalation Data from Phase 1 Trial of SY-1365 Demonstrating Proof-of-Mechanism at Tolerable Doses in Patients with Advanced Solid Tumors

Dose Selected for Ongoing Expansion Cohorts in Ovarian and Breast Cancers Supported by Tolerability Profile and Early Signs of Clinical Activity

Data Highlighted in Oral Plenary Session at EORTC-NCI-AACR Meeting

Management to Host Conference Call and Webcast at 4:00 PM ET Today

CAMBRIDGE, Mass., November 15, 2018 — Syros Pharmaceuticals (NASDAQ: SYRS), a leader in the development of medicines that control the expression of genes, today announced that data from the dose escalation portion of its Phase 1 trial of SY-1365, its first-inclass selective cyclin-dependent kinase 7 (CDK7) inhibitor, demonstrated proof-of-mechanism at tolerable doses in patients with advanced solid tumors. These data, the first clinical data reported on a selective CDK7 inhibitor, were highlighted in an oral plenary session at the 30th EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium in Dublin.

"These initial data on SY-1365 are highly encouraging," said Dejan Juric, M.D., Director of the Termeer Center for Targeted Therapies at Massachusetts General Hospital and a clinical investigator in the Phase 1 study of SY-1365. "Patient data from the SY-1365 dose escalation study confirm the unique mechanism-of-action of this agent and demonstrate an acceptable tolerability profile along with early signs of single-agent activity. These data, coupled with preclinical evidence showing robust anti-tumor activity in a range of relapsed and treatment-refractory cancer models, support the ongoing development of SY-1365 for patients who currently have few, if any, effective treatment options."

"As the first clinical data ever reported on a selective CDK7 inhibitor, these results mark an important milestone for SY-1365 and for the field of CDK7 inhibition," said David A. Roth, M.D., Syros' Chief Medical Officer. "We believe CDK7 inhibition is a potentially transformative new approach for treating many cancers that have eluded effective treatment with existing approaches. Now that we have demonstrated proof-of-mechanism at tolerable doses, we are committed to thoroughly exploring the potential of CDK7 inhibition for currently underserved patients. We are working to rapidly enroll the expansion cohorts in our ongoing Phase 1 study, focused initially on ovarian and breast cancers, while building on our leadership by advancing our highly selective and potent oral CDK7 inhibitor, SY-5609, as our next development candidate."

Dose Escalation Data

The dose escalation portion of the Phase 1 trial characterized the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of SY-1365 in patients with advanced solid tumors to establish a dose and regimen for the expansion portion of the trial. PD assays used to establish proof-of-mechanism included a CDK7 occupancy assay to evaluate SY-1365 binding and a custom gene expression assay to evaluate downstream transcriptional changes in patients. Preliminary anti-tumor activity was also assessed.

Enrollment in the dose escalation portion of the trial was completed in September. In total, 32 patients were treated with SY-1365 as a single agent at doses ranging from 2 mg/m² to 112 mg/m² using either a weekly or twice weekly dosing regimen. Patients were treated for three weeks out of each four-week cycle. Patients had a range of solid tumors, the most prevalent being ovarian cancer (eight patients), breast cancer (eight patients) and endometrial cancer (five patients). Patients' median age was 63 (ranging from 25 to 87), with a median of five prior therapies (ranging from one to 13). As of an October 15th data snapshot, the median treatment duration was 46.5 days (ranging from two to 147 days) and four patients remained on treatment.

Safety

- · Adverse events (AEs) were predominantly low-grade, reversible and generally manageable.
- The most commonly reported AEs were headache, nausea, vomiting and fatigue.
- · No neutropenia was reported.
- · Dose-limiting toxicities were headache, coronary vasospasm and fatigue.
- · A maximum tolerated dose was not defined.

Pharmacokinetics

- · Plasma PK exposures were linear over the doses tested.
- · No drug accumulation was observed with repeat dosing.

Proof-of-Mechanism

- · SY-1365 demonstrated dose-dependent effects on CDK7 occupancy and downstream gene expression changes in blood cells.
- At doses of 32 mg/m² and higher, CDK7 occupancy was greater than 50 percent when measured three days following dose administration, exceeding target occupancy levels in preclinical models that correlated with anti-tumor activity.
- CDK7 occupancy in blood cells was similar to target occupancy in tumor tissue biopsies available from two patients in the clinical trial.

Early Signs of Clinical Activity

As of the October 15th data snapshot, clinical activity per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria was observed in seven of the 19 patients (37%) who were evaluable for clinical responses, including:

 One patient with ovarian cancer in her fourth relapse who had a confirmed partial response (PR) after two cycles of treatment at the 80 mg/m² twice-weekly dose. The patient remained in PR at her CT assessment after six cycles and recently entered her seventh month on study treatment.

 Six additional patients who had stable disease, lasting between 50 and 127 days. Most of these patients received doses equal to or greater than 32 mg/m².

Based on these data, Syros selected a twice-weekly dose of 80 mg/m^2 of SY-1365 when administered as a single agent, and a once-weekly target dose of 80 mg/m^2 of SY-1365 when administered in combination with other agents, for further evaluation in the ongoing Phase 1 expansion cohorts in multiple ovarian and breast cancer patient populations.

Ongoing Expansion of Phase 1 Trial

Upon completing enrollment in the dose-escalation portion of the trial, Syros opened expansion cohorts to further assess the safety and anti-tumor activity of SY-1365 in multiple ovarian and breast cancer patient populations. The initial expansion strategy is based on preclinical data showing anti-tumor activity in these tumor types, a strong mechanistic rationale and high unmet need. The expansion cohorts are evaluating SY-1365: as a single agent in primary platinum-refractory ovarian cancer patients; as a single agent in ovarian cancer patients who have relapsed after three or more therapies; in combination with carboplatin in ovarian cancer patients who have relapsed after one or more prior therapies; and in combination with fulvestrant in patients with hormone-receptor positive (HR+) metastatic breast cancer who have progressed after treatment with a CDK4/6 inhibitor. An additional cohort is enrolling patients with any solid tumor accessible for biopsy to further evaluate the mechanism of action of SY-1365. Additional details about the trial can be found using the identifier NCT03134638 at www.clinicaltrials.gov.

The dose escalation data presented at the EORTC-NCI-AACR meeting is now available on the Publications and Abstracts section of the Syros website at www.syros.com.

Conference Call and Webcast

Syros will host a conference call today at 4:00 p.m. ET to discuss the data from the dose escalation portion of its Phase 1 trial.

The live call may be accessed by dialing (866) 595-4538 for domestic callers or (636) 812-6496 for international callers and referencing conference ID number: 4567679. A live webcast of the conference call will be available online on the Investors & Media section of the Syros website at www.syros.com. An archived replay of the webcast will be available for approximately 90 days.

About Syros Pharmaceuticals

Syros is pioneering the understanding of the non-coding regulatory region of the genome to advance a new wave of medicines that control the expression of genes. Syros has built a proprietary platform that is designed to systematically and efficiently analyze this unexploited region of DNA to identify and drug novel targets linked to genomically defined patient populations. Because gene expression is fundamental to the function of all cells, Syros' gene control platform has broad potential to create medicines that achieve profound

and durable benefit across a range of diseases. Syros is currently focused on cancer and monogenic diseases and is advancing a growing pipeline of gene control medicines. Syros' lead drug candidates are SY-1425, a selective RARα agonist in a Phase 2 clinical trial for genomically defined subsets of patients with acute myeloid leukemia and myelodysplastic syndrome, and SY-1365, a selective CDK7 inhibitor in a Phase 1 clinical trial for patients with ovarian and breast cancers. Syros is also developing a deep preclinical and discovery pipeline, including SY-5609, an oral CDK7 inhibitor, as well as programs in immuno-oncology and sickle cell disease. Led by a team with deep experience in drug discovery, development and commercialization, Syros is located in Cambridge, Mass.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including without limitation statements regarding the potential benefits of CDK7 inhibition and of SY-1365, alone or in combination with other therapeutic agents; the durability of clinical responses observed with SY-1365; the ability to enroll the expansion cohorts in the ongoing Phase 1 clinical trial and commence any future clinical studies of SY-1365; and the benefits of Syros' gene control platform. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "hope," "intend," "may," "plan," "potential," "predict," "project," "target," "should," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including Syros' ability to: advance the development of its programs, including SY-1365, under the timelines it projects in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; replicate scientific and non-clinical data in clinical trials; obtain and maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; obtain and maintain necessary regulatory approvals; identify, enter into and maintain collaboration agreements with third parties; manage competition; manage expenses; raise the substantial additional capital needed to achieve its business objectives: attract and retain gualified personnel; and successfully execute on its business strategies; risks described under the caption "Risk Factors" in Syros' Annual Report on Form 10-K for the year ended December 31, 2017, as updated in its Quarterly Reports on Form 10-Q for the quarters ended March 31, June 30 and September 30, 2018, each of which is on file with the Securities and Exchange Commission; and risks described in other filings that Syros makes with the Securities and Exchange Commission in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Syros expressly disclaims any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

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