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Syros Announces Update on Selective CDK7 Inhibitor Portfolio

Prioritizing Development of SY-5609, Its Oral CDK7 Inhibitor, and Discontinuing Further Development of SY-1365, Its Intravenous CDK7 Inhibitor

Expects to Initiate Phase 1 Trial of SY-5609 in First Quarter of 2020

Management to Host Conference Call at 8:30 a.m. ET Today

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today provided an update on its portfolio of selective cyclin-dependent kinase 7 (CDK7) inhibitors. The Company has decided to prioritize the development of its highly selective and potent oral CDK7 inhibitor, SY-5609, and to discontinue further development of SY-1365, its intravenous (IV) CDK7 inhibitor. Syros expects to initiate a Phase 1 clinical trial of SY-5609 in patients with select solid tumors in the first quarter of 2020.

SY-5609 inhibits CDK7 more selectively and potently than SY-1365 and has demonstrated greater anti-tumor activity than SY-1365 in multiple preclinical models. Furthermore, initial clinical activity and tolerability data from the expansion of the Phase 1 trial of SY-1365 did not support an optimal profile for patients, particularly in light of an increasing focus on oral targeted agents in cancer. As an oral molecule, Syros believes SY-5609 provides more flexibility in dosing and greater opportunity to sustain the levels of target coverage needed to improve treatment outcomes. Based on these factors, Syros has made a CDK7 portfolio decision to focus on SY-5609.

"We believe in selective CDK7 inhibition as a potentially transformative targeted approach for difficult-to-treat cancers," said Nancy Simonian, M.D., Chief Executive Officer of Syros. "SY-1365 was the first selective CDK7 inhibitor to enter clinical development, demonstrating proof-of-mechanism for this novel therapeutic approach and showing early signs of clinical activity. We have gained important insights from our work on SY-1365 that have informed our development strategy for SY-5609, including focusing on patient populations most likely to respond to a CDK7 inhibitor. We are prioritizing SY-5609 because we believe it has best-in-class potential and that it provides the greatest opportunity to realize the promise of selective CDK7 inhibition for patients."

SY-5609: An Oral, Highly Selective and Potent Non-Covalent CDK7 Inhibitor

SY-5609 has induced deep and sustained tumor growth inhibition, including complete regressions, in preclinical models of breast, ovarian and lung cancers at doses below the maximum tolerated dose. SY-5609 has also shown substantial anti-tumor activity in combination with fulvestrant in hormone receptor (HR)-positive breast cancer models that are resistant to CDK4/6 inhibitors. Importantly, SY-5609 showed greater tumor growth

inhibition than SY-1365 in preclinical models in which they were both studied, including those that were not responsive to SY-1365.

Syros is on track to complete investigational new drug application-enabling studies for SY-5609 by year-end. The Company expects to initiate a Phase 1 trial in patients with select solid tumors, including breast, lung and ovarian cancers and cancers of any histology defined by a specific molecular signature, in the first quarter of 2020. Syros plans to present new preclinical data on the pharmacokinetics, pharmacodynamics and anti-tumor activity of SY-5609 on October 29 at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston. The abstract for the presentation is available on the conference website at: <https://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=184>.

Initial data from expansion portion of Phase 1 trial of SY-1365

As of a planned September 30 data snapshot, 68 patients had been treated in the expansion portion of the Phase 1 trial of SY-1365, including 53 across the single-agent cohorts in patients with high-grade serous ovarian cancer (HGSOC), relapsed clear cell ovarian cancer and solid tumors of any histology available for biopsy, and 15 patients in the combination cohorts in HGSOC and metastatic CDK4/6 inhibitor-resistant HR-positive breast cancer.

Syros initiated the single-agent expansion cohorts at a dose of 80 mg/m² twice weekly and the combination cohorts at 53 mg/m² once weekly. During the expansion, peri-infusional adverse events (AEs) thought to be related to the IV administration of SY-1365 prompted evaluations of lower doses in the single-agent cohorts and extended infusion times across all the cohorts. Extended infusion times reduced peak drug concentrations and appeared to reduce the overall frequency and severity of peri-infusional AEs, including headache, nausea and vomiting.

The best response observed across the expansion cohorts was stable disease, as defined by RECIST criteria. Response-evaluable patients were primarily treated at doses of 53 and 64 mg/m². Of the 31 response-evaluable patients treated with single-agent SY-1365, 13 (42 percent) had stable disease. Of the 11 response-evaluable patients treated in the combination cohorts, seven (64 percent) had stable disease.

Based on preclinical and clinical data, Syros believes that sustaining the level of CDK7 target coverage needed to enhance clinical activity would require more frequent dosing, or a higher dose that would necessitate further lengthening the infusion to manage tolerability. Syros believes that either approach could create an overly burdensome dosing schedule for patients that can better be addressed with SY-5609.

Conference Call and Webcast:

Syros will host a conference call at 8:30 a.m. ET today to discuss this update on its CDK7 franchise and plans to prioritize the development of SY-5609.

To access the live call, please dial 866-595-4538 (domestic) or 636-812-6496 (international) and refer to conference ID 4578949. A webcast of the call will also be available on the Investors & Media section of the Syros website at www.syros.com. An archived replay will be available for approximately 30 days following the call.

About Syros Pharmaceuticals

Syros is redefining the power of small molecules to control the expression of genes. Based on its unique ability to elucidate regulatory regions of the genome, Syros aims to develop medicines that provide a profound benefit for patients with diseases that have eluded other genomics-based approaches. Currently focused on cancer and monogenic diseases, Syros is advancing a robust pipeline of development candidates, including SY-1425, a first-in-class oral selective RAR α agonist in a Phase 2 trial in a genomically defined subset of acute myeloid leukemia patients, and SY-5609, a highly selective and potent oral CDK7 inhibitor in investigational new drug application-enabling studies in cancer. Syros also has multiple preclinical and discovery programs in oncology and sickle cell disease. For more information, visit www.syros.com and follow us on Twitter (@SyrosPharma) and LinkedIn.

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 Syros' ability to complete IND-enabling preclinical studies by year-end and begin clinical development of SY-5609, including its plans to initiate a Phase 1 clinical trial of SY-5609 in the first quarter of 2020; the reporting of new preclinical data for SY-5609 at the AACR-NCI-EORTC meeting; the potential of SY-5609 to be a best-in-class CDK7 inhibitor; and Syros' ability to replicate preclinical data with SY-5609 in clinical studies; and the potential for selective CDK7 inhibition to be a transformative targeted approach for difficult-to-treat cancers. 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-5609, under the timelines it projects; demonstrate in clinical trials the requisite safety, efficacy and combinability of SY-5609; successfully progress SY-5609 through IND-enabling preclinical and toxicology studies; replicate scientific and non-clinical data in clinical trials; obtain and maintain patent protection for SY-5609 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, 2018 and Quarterly Report on Form 10-Q for the quarter ended June 30, 2019, 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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