December 10, 2017

Syros Announces Initial Clinical Data from Ongoing Phase 2 Trial of SY-1425 Showing Biological and Clinical Activity as Single Agent in Genomically Defined AML and MDS Patients

Clinical Activity Observed in 43% of Evaluable Relapsed or Refractory AML and Higher-Risk MDS Patients, Including Improvement in Blood Counts, Reduction in Leukemic Blasts and One Marrow Complete Response As Defined by IWG Criteria

Myeloid Differentiation Observed, Including Induction of CD38 in 85% of Evaluable Patients

Activity As Single Agent, Coupled with Preclinical Combination Data, Support Ongoing Phase 2 Trial of SY-1425 in Combination with Other Therapies

Initial Clinical Data from Cohorts Evaluating SY-1425 in Combination with a Hypomethylating Agent and with an Anti-CD38 Therapy Expected in 2018

Syros to Host Investor Event and Webcast on Monday, December 11 at 12:00 p.m. ET

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS), a biopharmaceutical company pioneering the discovery and development of medicines to control the expression of disease-driving genes, today announced initial clinical data from its ongoing Phase 2 trial of SY-1425, its first-in-class oral, selective retinoic acid receptor alpha (RARα) agonist, in genomically defined subsets of patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The data are being presented at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition.

“I’m encouraged with the single-agent activity and tolerability of SY-1425 in difficult-to-treat leukemia and MDS patients who have few treatment options,” said Joseph G. Jurcic, Professor of Medicine at Columbia University Medical Center and Director of the Hematologic Malignancies Section of the Division of Hematology/Oncology. “We saw improved blood counts and reduced blast counts in conjunction with differentiation of cancer cells in genomically defined patients. These data, along with the mechanistic and preclinical data supporting combinations with azacitidine and with daratumumab, suggest SY-1425 could be a meaningful combination agent with the potential to address a substantial unmet need for patients with AML and MDS.”

“The biologic and clinical activity seen in patients selected by our proprietary *RARA* and *IRF8* biomarkers provide validation of our platform’s ability to enrich for patients most likely to respond to gene control therapies,” said Nancy Simonian, M.D., Chief Executive Officer of

Syros. “These data support continued development of SY-1425 in combination, which will be our focus going forward. Our preclinical data showing the tumor-killing activity of SY-1425 in combination with azacitidine and with daratumumab support the ongoing development of SY-1425 in combination with these therapies, and we plan to present initial clinical data on these two combinations in 2018.”

Data from the Ongoing Phase 2 Clinical Trial
The ongoing Phase 2 clinical trial of SY-1425 is assessing the safety and efficacy as both a single agent and a combination agent in AML and MDS patients who are positive for either the *RARA* or *IRF8* biomarkers, or both. The data being presented at ASH are from two of the five cohorts in the ongoing trial. As of the data cutoff at the end of October 2017, 58 patients had been treated with SY-1425 in two single-agent cohorts, consisting of 29 patients in the relapsed or refractory AML and higher-risk MDS cohort and 29 patients in the lower-risk transfusion-dependent MDS cohort.

The relapsed or refractory AML and higher-risk MDS cohort had a median age of 72 years with more than half the patients having poor risk cytogenetics and 45% having two or more prior therapies, and the lower-risk MDS cohort had a median age of 76 years. Target enrollment has been reached in both cohorts.

Initial Safety Data

- Chronic daily dosing of SY-1425 administered at 6 mg/m^2 orally divided in two doses was generally well-tolerated, with a median treatment duration of 80 days, and patients treated up to eight months and remaining on study.
- The majority of adverse events (AEs) were Grade 1 or Grade 2.
- Across all grades and causality, the most commonly reported AEs included hypertriglyceridemia (36%), fatigue (31%), and dermatologic effects (28%).
- The most common Grade 3 or 4 AE was hypertriglyceridemia (16%).

Initial Clinical Activity Data

As of the data cutoff, 48 patients were evaluable for response assessment, including 23 patients in the relapsed or refractory AML and higher-risk MDS cohort and 25 patients in the lower-risk transfusion-dependent MDS cohort.

- Ten of the 23 (43%) evaluable relapsed or refractory AML and higher-risk MDS patients and two of the 25 (8%) evaluable transfusion-dependent lower-risk MDS patients had evidence of clinical activity, including:.
    - Nine with improvements in hematological parameters. Of those, four achieved hematological improvement lasting at least eight weeks, as defined by Revised International Working Group (IWG) criteria.
    - Five with reductions in bone marrow blasts. Of those, one relapsed or refractory higher-risk MDS patient achieved a marrow complete response as defined by IWG criteria. The patient had been on treatment 238 days and remained on treatment as of the data cutoff.
- 13 of the 23 (57%) evaluable relapsed or refractory AML and higher-risk MDS patients

had stable disease.

- 11 of 13 (85%) of patients with pre- and post-treatment immunophenotyping samples showed increased expression of CD38, a marker of cell differentiation, on bone marrow blasts after one 28-day cycle of treatment.
- No patients with lower-risk MDS achieved transfusion independence.

Additionally, myeloid cell differentiation in the bone marrow, as measured by morphologic evaluation, FISH analysis and immunophenotyping, was observed, consistent with the underlying mechanism of action of SY-1425 as a differentiating agent. The induction of CD38 observed in bone marrow blasts from patients treated with SY-1425 supports the combination cohort with daratumumab recently added to the Phase 2 trial.

As presented at the European School of Haematology's 4th International Conference on Acute Myeloid Leukemia in October 2017, approximately 40% of 201 patients screened for the clinical trial as of the end of August 2017 were biomarker-positive, including approximately one-third of relapsed or refractory AML and higher-risk MDS patients. In blood samples taken from patients upon screening and treated *ex vivo* with SY-1425, a positive biomarker status was significantly correlated with SY-1425 induced myeloid cell differentiation, supporting the predictive value of the biomarker test for patient selection.

Preclinical Combination Data for SY-1425
SY-1425 has shown synergistic tumor-killing activity in combination with azacitidine, a standard-of-care therapy in AML and MDS, as well as with daratumumab, an anti-CD38 antibody approved to treat multiple myeloma, in preclinical models of *RARA* biomarker-positive AML. In combination with azacitidine, SY-1425 demonstrated greater clearance of tumor cells in bone marrow and other tissues and greater depth and duration of tumor response, compared to either azacitidine or SY-1425 alone. In combination with daratumumab, SY-1425 triggered robust immune cell-mediated tumor death. Notably, AML cells do not normally express high levels of CD38. Syros has shown that by inducing CD38 expression, SY-1425 sensitizes biomarker-positive AML models to the tumor-killing effects of daratumumab.

Clinical Development Plans for SY-1425
Syros plans to focus its ongoing Phase 2 clinical trial on assessing the safety and efficacy of SY-1425 in combination with other therapies. Syros is continuing to enroll patients in a cohort evaluating SY-1425 in combination with azacitidine in newly diagnosed AML patients who are not suitable candidates for standard chemotherapy. Syros recently added a cohort in relapsed or refractory AML and higher-risk MDS patients to evaluate SY-1425 in combination with daratumumab and expects to begin enrolling patients in that cohort in early 2018. All patients enrolled or to be enrolled in the trial are prospectively selected using the Company's *RARA* or *IRF8* biomarkers. Syros expects to report initial clinical data from each combination cohort in 2018. Syros does not plan to pursue further development of SY-1425 as a single agent and is stopping enrollment in the single-agent cohort in newly diagnosed AML patients who are not suitable candidates for standard chemotherapy. Additional details about the trial can be found using the identifier NCT02807558 at www.clinicaltrials.gov.

Investor Event and Webcast Information
Syros will host an investor event on Monday, December 11 beginning at 12:00 p.m. ET in Atlanta to discuss the initial SY-1425 clinical data presented at ASH. The event can be

accessed by dialing 866-595-4538 (domestic) or 636-812-6496 (international) and providing the passcode 8887999. A live webcast will also be available and can be accessed under "Events & Presentations" in the Investors section of the Company's website at https://ir.syros.com. A replay of the webcast will be available approximately two hours after the event and will be available for 30 days following the event.

About Syros Pharmaceuticals
Syros Pharmaceuticals is pioneering the understanding of the non-coding region of the genome to advance a new wave of medicines that control expression of disease-driving genes. Syros has built a proprietary platform that is designed to systematically and efficiently analyze this unexploited region of DNA in human disease tissue 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 immune-mediated 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 advanced solid tumors, including transcriptionally dependent cancers such as triple negative breast, small cell lung and ovarian cancers. 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 therapeutic benefit of SY-1425 in combination with azacitidine and daratumumab in AML and MDS patients; the reporting of clinical data from the combination cohorts of the ongoing Phase 2 clinical trial of SY-1425 in 2018; the prevalence of the *RARA* and *IRF8* biomarkers in AML and MDS patients; the ability to identify an appropriate dose and schedule to support expansion of the Phase 1 clinical trial of SY-1365, and the benefits of Syros' gene control platform. The words ‘‘anticipate,’’ ‘‘believe,’’ ‘‘continue,’’ ‘‘could,’’ ‘‘estimate,’’ ‘‘expect,’’ ‘‘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-1425, 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; successfully develop a companion diagnostic test to identify patients with the *RARA* and *IRF8* biomarkers; 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' Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, 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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