Syros Presents New Data from Phase 2 Clinical Trial of SY-1425 and Announces Plans to Initiate Registration-Enabling Trial in MDS and Randomized Phase 2 Trial in AML

61% Composite CR Rate in RARA-Positive Newly Diagnosed Unfit AML Patients, with Median Overall Survival of 18 Months Among Responders

Plan to Initiate Registration-Enabling Phase 3 Trial of SY-1425 in Combination with Azacitidine in Newly Diagnosed Higher-Risk MDS in 1Q 2021

Plan to Initiate Randomized Phase 2 Trial of SY-1425 as Part of Triplet Regimen with Venetoclax and Azacitidine in Newly Diagnosed Unfit AML in 2H 2021

Management to Host Conference Call at 4:30 p.m. ET Today

CAMBRIDGE, Mass., December 5, 2020 – Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today announced new clinical data from its Phase 2 trial evaluating SY-1425, its first-in-class selective retinoic acid receptor alpha (RARα) agonist, in combination with azacitidine in two acute myeloid leukemia (AML) patient populations. The data is being presented today in oral presentations at the 62nd American Society of Hematology (ASH) Annual Meeting. In a separate poster presentation on Monday, Syros will present translational data highlighting the potential of SY-1425 to benefit newly diagnosed unfit AML patients who may be resistant to the standard-of-care combination of venetoclax plus azacitidine.

“The data that continue to emerge from the Phase 2 trial of SY-1425 are compelling,” said Stéphane De Botton, M.D., Head of Acute Myeloid Malignancies at Institut Gustave Roussy and a clinical investigator in the trial. “SY-1425 in combination with azacitidine demonstrates high response rates, rapid onset of action, meaningful durability and favorable tolerability in RARA-positive newly diagnosed unfit AML patients. Despite recent advances, one-third of unfit AML patients still don’t respond to the standard-of-care regimen in the upfront setting and what we are now learning is that most of these patients may be RARA-positive. Taken together, these data support the potential of SY-1425 to become an important targeted therapy for RARA-positive AML patients, as well as for patients with a closely related hematologic malignancy known as higher-risk myelodysplastic syndrome.”

“The new data presented today strengthen our conviction that SY-1425 has the potential to become the foundation of care for all RARA-positive patients,” said David A. Roth, M.D., Chief Medical Officer of Syros. “Based on these results, we are excited to launch our planned registration-enabling Phase 3 trial in newly diagnosed higher-risk MDS patients, which puts us on track for a potential new drug application in 2024, and a randomized Phase 2
clinical trial evaluating SY-1425 as part of a triplet regimen with venetoclax and azacitidine in newly diagnosed unfit AML patients.”

Promising New Data from Phase 2 Trial of SY-1425 in RARA-positive AML
Syros presented new data from its fully enrolled Phase 2 trial evaluating the safety and efficacy of SY-1425 in combination with azacitidine in newly diagnosed AML patients who are not suitable candidates for standard chemotherapy, as well as in RARA-positive relapsed or refractory (R/R) AML patients.

Mature Data in Newly Diagnosed Unfit AML
As of October 1st, 51 newly diagnosed unfit AML patients, including both RARA-positive and RARA-negative patients, were eligible for a safety analysis. Eighteen RARA-positive were evaluable for clinical response. In those patients, the data showed that:

- Overall response rate (ORR) was 67% (12/18), with a composite CR rate of 61%, (11/18) including nine patients (50%) achieving a complete response (CR), two patients (11%) achieving a complete response with incomplete blood count recovery (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.
- Median time to initial response was 1.2 months.
- Median duration of response was 10.8 months, and median overall survival (OS) among patients who achieved a CR or CRi was 18 months.
- 86% (6/7) of patients who were transfusion dependent at baseline became transfusion independent, and 67% (12/18) of patients achieved or maintained transfusion independence.
- SY-1425 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.

Syros will also present new translational data demonstrating that most RARA-positive newly diagnosed unfit AML patients have a monocytic disease phenotype that is highly correlated with resistance to upfront treatment with venetoclax and azacitidine. These data suggest that the RARA biomarker not only selects for patients who are more likely to respond to treatment with SY-1425 but also for patients who are less likely to respond to treatment with venetoclax and azacitidine.

Data in Relapsed or Refractory AML
As of October 1st, 28 RARA-positive R/R AML patients were eligible for safety analysis and 21 were evaluable for clinical response. In those patients, the data showed:

- ORR was 19% (4/21), consisting of one CRc, two CRi and one MLFS.
  - In HMA and venetoclax naïve patients, the ORR was 43% (3/7 patients).
- Median OS was 5.9 months.
• 30% (6/20) achieved or maintained transfusion independence, including 27% (3/11) of patients who were transfusion dependent at baseline.

• SY-1425 in combination with azacitidine was also generally well-tolerated in this patient population.

Advancing SY-1425 in Newly Diagnosed HR-MDS and Unfit AML
Based on the encouraging clinical activity and favorable safety and tolerability profile of SY-1425 in combination with azacitidine as well as an assessment of ongoing areas of high unmet need within the evolving treatment landscape, Syros plans to advance SY-1425 in combination with azacitidine into a registration-enabling Phase 3 trial in RARA-positive newly diagnosed higher-risk myelodysplastic syndrome (HR-MDS) patients. HR-MDS is a hematologic malignancy that is closely related to AML, and as in AML, about 30 percent of HR-MDS patients are RARA-positive.

Based on feedback from the U.S. Food and Drug Administration, Syros plans to enroll approximately 190 RARA-positive newly diagnosed HR-MDS patients in the double-blind placebo-controlled trial, randomized 2:1 to receive SY-1425 in combination with azacitidine or placebo with azacitidine, respectively. The primary endpoint of the trial will be the CR rate, which, depending on the data outcome, could support accelerated or full approval in this patient population. Syros expects to initiate the Phase 3 trial in the first quarter of 2021.

In addition, Syros plans to advance SY-1425 in combination with venetoclax and azacitidine in RARA-positive newly diagnosed unfit AML patients. The trial is designed with a single-arm safety lead-in to confirm the dosing regimen of the triplet to be used in the randomized portion of the Phase 2 trial, which will evaluate the safety and efficacy of SY-1425 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 therapy in patients who don’t respond to venetoclax and azacitidine. Syros expects to initiate the Phase 2 trial in the second half of 2021.

Conference Call Information
Syros will host a conference call today at 4:30 p.m. ET to discuss these data, as well as its acquisition of SY-2101, a clinical-stage drug candidate for the treatment of acute promyelocytic leukemia, from Orsenix, LLC, which was also announced today.

To access the live conference call, please dial 866-595-4538 (domestic) or 636-812-6496 (international), and refer to conference ID 1264464. 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 of the webcast will be available for approximately 30 days following the presentation.

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. Syros is advancing a robust clinical-stage pipeline, including SY-1425, a first-in-class oral selective RARα agonist in RARA-positive patients with higher-risk myelodysplastic syndrome and acute myeloid leukemia, SY-2101, a novel oral form of arsenic trioxide in patients with acute promyelocytic leukemia, and SY-5609, a highly selective and potent oral CDK7 inhibitor in patients with select solid tumors. Syros also has multiple preclinical and discovery programs in oncology and monogenic diseases. 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 the promise of the new data from Syros’ Phase 2 clinical trial of SY-1425, the plans to initiate a registration-enabling Phase 3 trial of SY-1425 in combination with azacitidine in higher-risk MDS and a randomized Phase 2 trial of SY-1425 in combination with venetoclax and azacitidine with a safety lead-in in newly diagnosed unfit AML, the potential of SY-1425 to benefit patients with hematologic malignancies and to become the foundation of care for all RARA-positive patients, and the predictive value of the RARA biomarker. 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-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 SY-1425; sustain the response rates and durability of response seen to date with SY-1425 in combination with azacitidine; successfully develop a companion diagnostic test to identify patients with the RARA biomarker; obtain and maintain patent protection for SY-1425 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, 2019 and Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, 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. In addition, the extent to which the COVID-19 outbreak continues to impact Syros’ workforce and its clinical trial operations activities, and the operations of the third parties on which Syros relies, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the outbreak, additional or modified government
actions, and the actions that may be required to contain the virus or treat its impact. 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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