January 10, 2022

Syros Announces Clinical Updates and 2022 Goals to Support its Advancement to a Fully Integrated Biopharmaceutical Company

Initiated Expansion Cohort of SY-5609 with Chemotherapy in Pancreatic Cancer Patients

Expects to Report Data from Three Clinical Trials Across Hematology and Selective CDK Inhibitor Programs in 2022

Now Expects to Initiate Phase 1 Single Agent Trial of SY-5609 in Hematologic Malignancies in 2H 2022

Expects to Nominate Development Candidate from CDK12 Program in 2H 2022

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 clinical development programs and outlined its strategic priorities and upcoming expected milestones.

“2022 promises to be a transformative year as we continue to advance our studies of tamibarotene, SY-2101, and SY-5609. We are looking forward to three clinical data readouts this year as well as pivotal data from the SELECT-MDS-1 trial in late 2023 or early 2024,” said Nancy Simonian, M.D., Syros’ Chief Executive Officer. “Additionally, in the second half of this year we expect to nominate our new development candidate from our CDK12 program, highlighting the productivity of our gene control discovery engine and our expertise in CDK inhibition. Together, we believe these upcoming milestones will provide insight into the clinical potential of our development-stage assets and lay the foundation for our long-term growth as we advance Syros into a fully integrated biopharmaceutical company.”

Dr. Simonian continued, “We are pleased with our recent interactions with the U.S. Food and Drug Administration on the Phase 3 clinical trial design of SY-2101, which we now expect to initiate in the first quarter of 2023. In addition, based on preclinical data that supports CDK7 inhibition’s potential across a range of hematologic malignancies, we expect to start in the second half of this year a Phase 1 single agent study of SY-5609 in patients with relapsed blood cancers, including B-cell lymphomas, prior to moving into specific indications. We are excited to be the first company to advance a CDK7 inhibitor into hematology clinical development. The trial results have potential to benefit a broader patient population as well as demonstrate CDK7 inhibition as a novel approach for many difficult-to-treat hematologic cancers.”

CLINICAL PROGRAM UPDATES AND UPCOMING MILESTONES

Targeted Hematology

Tamibarotene: Oral RARa agonist

Syros is evaluating tamibarotene in patients with RARA-positive newly diagnosed higher-risk myelodysplastic syndrome (HR-MDS). The Company expects to report data from the ongoing SELECT-MDS-1 Phase 3 trial evaluating tamibarotene in combination with azacitidine in HR-MDS in the fourth quarter of 2023 or first quarter of 2024, with a potential NDA filing expected in 2024.

Syros is also evaluating tamibarotene for the treatment of patients with RARA-positive newly diagnosed unfit acute myeloid leukemia (AML). The Company expects to report data from the safety lead-in portion of the ongoing SELECT-AML-1 Phase 2 trial evaluating tamibarotene in combination with azacitidine and venetoclax in the second half of 2022.

SY-2101: Oral arsenic trioxide (ATO)

Syros is evaluating SY-2101 in patients with newly diagnosed acute promyelocytic leukemia (APL). The Company expects to report PK and safety data from its ongoing dose confirmation trial in mid-2022. The feedback from a Type C meeting with the U.S. Food and Drug Administration (FDA) in November 2021 continues to support molecular complete response rate as the primary endpoint for accelerated approval and event free survival as the primary endpoint for full approval, in each case compared to historic IV ATO data. Additionally, based on the feedback, Syros now expects the trial to enroll approximately 215 patients randomized two to one to receive SY-2101 or intravenously administered (IV) ATO. The IV ATO arm will allow safety and tolerability comparisons. Syros now expects to initiate the Phase 3 trial in the first quarter of 2023 and to announce data in 2025.

Selective CDK Inhibition

SY-5609: Oral CDK7 inhibitor

In the fourth quarter of 2021, Syros initiated the expansion cohort evaluating SY-5609 in combination with chemotherapy in patients with second-line metastatic pancreatic cancer. The cohort is expected to enroll approximately 50 pancreatic cancer patients who have progressed following first-line treatment with FOLFIRINOX. Patients will receive either SY-5609 in combination with gemcitabine, or SY-5609 in combination with gemcitabine and nab-paclitaxel, at the approved doses of the combination agents. The study will evaluate safety and tolerability, as well as efficacy measures such as disease control rate and progression free survival. Syros expects to report safety lead-in data of SY-5609 in combination with chemotherapy in the second half of 2022.

Syros also plans to evaluate the potential of SY-5609 in hematologic tumors. Based on mechanistic rationale and preclinical data, which support the potential of CDK7 inhibition in a broad range of blood cancers, Syros will evaluate the maximum tolerated dose of SY-5609 in patients with relapsed hematologic malignancies, including B-cell lymphomas, such as mantle cell lymphoma, before starting a focused expansion cohort. The Phase 1 trial is expected to begin in the second half of 2022, with data expected mid-2023, which will inform further development in specific hematologic cancers.

In August 2021, Syros entered into an agreement with Roche to explore SY-5609 in combination with atezolizumab in patients with BRAF-mutant colorectal cancer (CRC), and Roche plans for this arm of its ongoing Phase 1/1b INTRINSIC trial to be open for enrollment in the first half of this year. Under the terms of this agreement, Roche is the sponsor of the trial and Syros is supplying SY-5609.

Gene Control Discovery Engine

Syros announced today that the next development candidate from its gene control discovery engine will be a CDK12 inhibitor. Syros plans to nominate this candidate in the second half of 2022.

Syros also announced today that small molecule inhibitors of CDK11 and WRN are the focus of two additional oncology programs in discovery.

Financial Guidance

Based on its current operating plans, Syros expects that its existing cash, cash equivalents and marketable securities will be sufficient to fund its anticipated operating expenses and capital expenditure requirements into 2023.

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: tamibarotene, 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 and blood cancers. 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 Syros' clinical development plans, including with respect to tamibarotene, SY-2101 and SY-5609, the potential for Syros' clinical programs to result in new standards of care, the potential of SY-5609 to address a range of hematologic malignancies and patient populations, the timing of anticipated data readouts from Syros' clinical trials, the timing to initiate the Phase 3 clinical trial of SY-2101 in APL and the trial of SY-5609 in hematologic malignancies, the potential for Syros's product candidates to obtain regulatory approval, the timing of nomination of Syros' next development candidate, and the sufficiency of Syros' capital resources to fund its operating expenses and capital expenditure requirements into 2023. 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 tamibarotene, SY-2101 and SY-5609, 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; sustain the response rates and durability of response seen to date with its drug candidates; successfully develop a companion diagnostic test to identify patients with the RARA biomarker; 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, 2020 and Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, 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 pandemic 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 pandemic, 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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