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Syros Acquires Clinical-Stage Drug Candidate for Acute Promyelocytic Leukemia, Expanding Its Pipeline of Targeted Therapies for Hematologic Malignancies

Oral Arsenic Trioxide has Potential to Reduce Treatment Burden of Standard-of-Care Regimen that Cures Most Patients

Dose Confirmation Study Expected to Begin in Second Half of 2021, Followed by Registration-Enabling Phase 3 Trial in 2022

$90.5 Million Strategic Financing Led by Bain Capital Life Sciences Extends Cash Runway through Multiple Expected Value Drivers into Second Half of 2022

Management to Host Conference Call at 4:30 p.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 announced that it has acquired from Orsenix, LLC (Orsenix) all of its assets related to SY-2101, formerly known as ORH-2014, a novel oral form of arsenic trioxide (ATO). SY-2101 represents a strategic opportunity to leverage Syros' expertise and capabilities to advance its growing footprint in hematologic disorders, with a targeted clinical-stage drug candidate that has the potential to dramatically reduce the treatment burden of a standard-of-care regimen for newly diagnosed acute promyelocytic leukemia (APL).

"It's rare to talk about cures in cancer," said Nancy Simonian, M.D., Chief Executive Officer of Syros. "The IV formulation of ATO is part of a treatment regimen that cures most APL patients, but it is extremely burdensome with lengthy infusions over a nearly yearlong course of treatment. We believe an oral form that offers similar efficacy while dramatically reducing the treatment burden on these patients could quickly become a new standard-of-care. SY-2101 is also highly complementary to our efforts with SY-1425 in AML and MDS, positioning us for potential new drug applications for both programs in 2024. With the strategic financing announced today, we believe we are well-funded to advance our growing portfolio of product candidates across multiple patient populations to accelerate our vision of becoming a fully integrated biopharmaceutical company."

A Potential New Standard-of-Care Therapy

SY-2101 is in development for the treatment of APL, a subtype of acute myeloid leukemia (AML) defined by a fusion of the *RARA* and *PML* genes. An intravenously administered

formulation of ATO is approved for use in combination with All-Trans-Retinoic-Acid (ATRA) in newly diagnosed APL and, while curative in approximately 80-90% of patients, its administration requires up to 140 two- to four-hour infusions over the typical course of induction and consolidation treatment.

Because SY-2101 is dosed orally once daily, it has the potential to become the standard-of-care frontline therapy for APL by providing comparable efficacy with a substantially more convenient option that reduces the treatment burden on patients, improving access, and lowering costs to the healthcare system. In a Phase 1 clinical trial, led by investigators at the M.D. Anderson Cancer Center, SY-2101 demonstrated bioavailability, pharmacokinetic (PK) exposures similar to IV ATO, and a generally well-tolerated safety profile.

Clinical Development Plans for SY-2101

Syros plans to initiate a dose confirmation study of SY-2101 in the second half of 2021. Following confirmation of a dose that demonstrates comparable PK to IV ATO, Syros intends to initiate a registration-enabling Phase 3 trial in patients with newly diagnosed APL in 2022. Based on interactions between Orsenix and the U.S. Food and Drug Administration (FDA), Syros believes molecular complete response rate and event-free survival in comparison to historical control data with IV ATO would support accelerated and full approval, respectively. If successful, Syros believes it could file a New Drug Application (NDA) with the FDA in 2024.

SY-2101 has orphan drug designation in the United States for the treatment of APL and Europe for the treatment of AML.

Acquisition Details

Under the terms of the asset purchase agreement, Syros has acquired all assets related to the development and commercialization of SY-2101, including intellectual property, clinical and preclinical data, the regulatory dossier, and product inventory. Syros has made an upfront cash payment of $12 million to Orsenix. In addition, Orsenix is eligible to receive a $6 million regulatory milestone related to the development of SY-2101 in APL and commercial milestones of up to $10 million. Orsenix is also eligible to receive single-digit million milestone payments related to the development of SY-2101 in indications other than APL.

Financing Details

Syros also announced today that it has entered into a definitive agreement for the sale of its equity securities in a private placement to a group of institutional accredited investors led by Bain Capital Life Sciences with participation from Ally Bridge Group, Omega Funds, OrbiMed, EcoR1 Capital, and Samsara BioCapital. The agreement provides for the sale of an aggregate of 10,312,500 shares of Syros' common stock and, in lieu of shares of common stock, pre-funded warrants (Pre-Funded Warrants) to purchase an aggregate of 1,000,000 shares of common stock, and accompanying warrants (Warrants) to purchase an aggregate of up to 2,828,125 additional shares of common stock (or Pre-Funded Warrants in lieu thereof) at a price of $8.00 per share and accompanying Warrant (or $7.99 per Pre-Funded Warrant and accompanying Warrant). The price per Pre-Funded Warrant and accompanying Warrant represents the price of $8.00 per share and accompanying Warrant

to be sold in the private placement, minus the $0.01 per share exercise price of each such Pre-Funded Warrant. The exercise price of the Warrants is $11.00 per share, or if exercised for a Pre-Funded Warrant in lieu thereof, $10.99 per Pre-Funded Warrant (representing the Warrant exercise price of $11.00 per share minus the $0.01 per share exercise price of each such Pre-Funded Warrant). The Warrants are exercisable at any time during the period beginning six months following the closing date of the private placement and ending on the fifth anniversary of the closing. The Pre-Funded Warrants are exercisable at any time after their original issuance and will not expire. The gross proceeds from the sales of common stock and Pre-Funded Warrants are expected to be $90.5 million, before deducting offering expenses. The private placement is expected to close on or about December 8, 2020, subject to the satisfaction of customary closing conditions.

The securities to be sold in the private placement have not been registered under the Securities Act of 1933, as amended (Securities Act), or any state or other applicable jurisdiction's securities laws, and may not be offered or sold in the United States absent registration or an applicable exemption from the registration requirements of the Securities Act and applicable state or other jurisdictions' securities laws.

This press release shall not constitute an offer to sell or the solicitation of an offer to buy these securities, nor shall there be any offer, solicitation or sale of these securities in any jurisdiction in which such offer, solicitation or sale would be unlawful.

Updated Financial Guidance

As a result of these transactions, Syros expects to have sufficient funds for planned operating expenses and capital expenditure requirements into the second half of 2022.

Conference Call Information

Syros will host a conference call today at 4:30 p.m. ET to discuss its acquisition of SY-2101, as well as the new data for SY-1425, which were presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition.

To access the live conference call, please dial 866-5954538 (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 Acute Promyelocytic Leukemia

APL is a well-defined subset of AML caused by the formation of an abnormal fusion gene, *PML/RARA*. This fusion gene leads to the overproduction of immature white blood cells called promyelocytes and the underproduction of healthy blood cells. Signs, symptoms and complications of APL include abnormal bleeding and bruising, anemia, fatigue, and increased risk of infection. APL makes up about 10% of AML cases, with an annual incidence of approximately 2,000 patients in the United States and Europe.

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 potential of SY-2101 to substantially reduce the treatment burden for newly-diagnosed APL patients and to become a standard-of-care, Syros's clinical development plans, including with respect to SY-1425 and SY-2101, and the anticipated primary endpoints for clinical trials, the strategic opportunity represented by the acquisition of SY-2101 and the intention to leverage Syros' existing infrastructure to develop SY-2101 and SY-1425, the potential submission of new drug applications and the likelihood of regulatory approval, the commercial promise of Syros' clinical programs, the use of proceeds from the private placement, the amount of proceeds expected from the private placement and upon the exercise of Warrants and Pre-Funded Warrants, the anticipated closing date for the private placement, and the sufficiency of Syros' capital resources to fund the acquisition and updated operating expenses and capital expenditure requirements into the second half of 2022. 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 and SY-2101, 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; complete the closing for the private placement; 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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