Syros Announces First Patient Enrolled in Phase 2 Clinical Trial of SY-1425 in Genomically Defined Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome

CAMBRIDGE, Mass., September 22, 2016 – Syros Pharmaceuticals (NASDAQ: SYRS) announced today that the first patient has been dosed in the Phase 2 clinical trial of its lead drug candidate, SY-1425, a first-in-class selective retinoic acid receptor alpha (RARα) agonist, in genomically defined subsets of patients with relapsed or refractory acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS) identified using a novel biomarker discovered by its gene control platform.

“This is an important milestone for Syros and for patients,” said David A. Roth, M.D., Chief Medical Officer of Syros. “There has been little improvement in the treatment of AML and MDS for the past 20 years, and survival rates for these patients lag behind many other blood cancers. Treatment with SY-1425 represents a promising therapeutic strategy for subsets of AML and MDS patients with a novel biomarker that we discovered using our gene control platform. Our pioneering approach is designed to advance a new wave of medicines to control the expression of disease-driving genes in genomically defined subsets of patients to provide them with a profound and durable clinical benefit. Our goal is to rapidly advance this first-in-class therapy for these currently underserved patients."

Using its gene control platform, Syros discovered subsets of AML and MDS patients whose tumors have a highly specialized regulatory region of non-coding DNA, known as a super-enhancer, that is associated with the *RARA* gene, which codes for the RARα transcription factor. The super-enhancer is believed to lead to over-production of the RARα transcription factor, locking cells in an immature, undifferentiated and proliferative state. Syros further investigated this unique biology directly in patient tissues and conducted preclinical studies showing that the *RARA* super-enhancer is predictive of response to treatment with SY-1425 in preclinical models of AML. Based on that data, Syros is implementing a biomarker strategy for its Phase 2 trial that selects a subset of approximately 25 percent of AML and MDS patients who may respond to treatment with SY-1425.

“The prognosis for these patients is poor, and targeted approaches like SY-1425 offer hope for much-needed new therapies that attack the underlying biology of the disease and hopefully allow patients to live longer without the toxicities of traditional chemotherapy,” said Rachel J. Cook, M.D., M.S., assistant professor of medicine at Oregon Health & Science University and an investigator in the trial. “We’re pleased to have enrolled the first patient in this clinical trial and look forward to further investigating SY-1425 for this newly identified subset of AML and MDS patients.”

The Phase 2 clinical trial is a multi-center, open-label trial exploring safety and efficacy in relapsed or refractory AML or high-risk MDS patients who have been prospectively selected using the Company's biomarker strategy. The trial is expected to enroll approximately 40 patients, and the primary endpoint of the trial will be overall response rate. The trial will also assess pharmacodynamic biomarkers, duration of response, safety and tolerability, and survival. Additional details about the trial can be found using the identifier NCT02807558 at www.clinicaltrials.gov.

SY-1425 is approved in Japan as Amnolake (tamibarotene) to treat a different form of AML known as acute promyelocytic leukemia (APL), in which it has a well-established efficacy and safety profile. Syros in-licensed SY-1425 to develop and commercialize it in North America and Europe for all cancers.

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 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, the Company's gene control platform has broad potential to achieve profound and durable benefit across a range of diseases. Syros is focused on cancer and immune-mediated diseases and is advancing a growing pipeline, including its lead drug candidates SY-1425, a selective RARα agonist for genomically defined subsets of patients identified by its platform, for a range of cancers including acute myeloid leukemia and myelodysplastic syndrome, and SY-1365, a selective CDK7 inhibitor for a range of blood cancers and solid tumors. 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 by the Company regarding: the potential therapeutic benefit of treatment with SY-1425 in subsets of AML and MDS patients identified with the Company's biomarker; the Company's strategies, plans and goals for SY-1425; and the potential benefits of the Company's 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; obtain and

maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; 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; and successfully execute on its business strategies; risks described under the caption "Risk Factors" in the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2016, which is on file with the Securities and Exchange Commission; and risks described in other filings that the Company 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 the Company expressly disclaims any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

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