Synlogic Announces SYNB1353 Achieves Proof of Mechanism for Treatment of Homocystinuria and Provides Business Update

November 30, 2022

Top-line Phase 1 data in healthy volunteers show that SYNB1353 reduces plasma methionine by consuming methionine in the GI tract

SYNB1353 has been granted Orphan Drug Designation (ODD) from the FDA for the treatment of homocystinuria (HCU)

Company confirms expectations for proof-of-concept data for SYNB8802 in enteric hyperoxaluria before year-end and Phase 3 initiation of SYNB1934 for PKU in H1 2023

Organization streamlined to best support strategic priorities

CAMBRIDGE, Mass., Nov. 30, 2022 (GLOBE NEWSWIRE) -- Synlogic, Inc. (Nasdaq: SYBX), a clinical-stage biotechnology company developing medicines for metabolic and immunological diseases through its proprietary approach to synthetic biology, today announced that SYNB1353 has achieved proof of mechanism and positive results in a Phase 1 study in healthy volunteers treated with multiple ascending doses of SYNB1353. SYNB1353 is an orally administered, non-systemically absorbed drug candidate designed to consume methionine in the GI tract for the potential treatment of homocystinuria (HCU).

The Company also shared that the FDA has granted Orphan Drug Designation (ODD) to SYNB1353 for the treatment of HCU. ODD is granted by the FDA to drugs or biologics intended to treat a rare disease or condition, which generally affects less than 200,000 individuals in the U.S. ODD-granted therapies entitle companies to development incentives including tax credits for qualified clinical trials, user fee exemptions, and the potential for seven years of market exclusivity after approval.

Following the recent successful completion of the Company's Phase 2 study in phenylketonuria (PKU), and now with proof of mechanism achieved in the Phase 1 for HCU, the Company also shared a plan to focus on advancing its clinical stage and prioritized preclinical research programs.

Top-line Findings:

The goal in treating HCU is to reduce and control severely elevated levels of total homocysteine (tHcy), thereby reducing risk of acute, potentially life-threatening blood clots and chronic, multisystem complications. A diet low in methionine, a precursor to homocysteine, is standard in HCU; SYNB1353 is engineered to metabolize methionine in the GI tract to prevent its absorption and conversion into homocysteine. An objective of this Phase 1 study was to assess effects of methionine consumption by SYNB1353 in healthy volunteers, assessed primarily through a dietary model using a methionine meal challenge. This dietary model was intended to capture in healthy volunteers a transient elevation in methionine following a meal challenge, in order to demonstrate proof of mechanism of consumption of methionine by SYNB1353.

Top-line findings include:

- Dosing of SYNB1353 resulted in a reduction in plasma methionine when measured over 24-hours as area under the curve (AUC) following a methionine meal challenge.
- SYNB1353 was generally well tolerated. Adverse events (AEs) were all mild to moderate, transient, and predominantly GI in nature.
- Frequency and severity of GI-related AEs were similar in the active and control group.

"We are pleased to share this important milestone for our HCU program and our second positive data readout for the Synthetic Biotic platform in 2022," said Aoife Brennan, M.B. Ch.B., Synlogic President and Chief Executive Officer. "HCU is an extremely challenging disease and patients need new treatment options. The difficulty of current treatments, including the low methionine diet, results in many patients remaining at risk of life-threatening consequences. We are very pleased that SYNB1353 has demonstrated promise to provide a safe, oral treatment option through its novel approach, and look forward to its continued development, including evaluation for proof of concept in HCU patients."

"With today's favorable study results, we are also sharing news of our realigned organization, now optimized to execute against our strategic priorities and create a stronger, more agile company. We are grateful for the dedication of our departing colleagues to our mission. Their tremendous contributions have helped us pioneer Synthetic Biotics, and most of all, provided hope to many patients and families in need of new treatments."

The SYNB1353 Phase 1 Study

The phase 1 study included a double-blind, dose-escalation, randomized, placebo-controlled, multiple-ascending dose (MAD) design in healthy volunteers in an inpatient setting. The objectives were to evaluate the safety and tolerability, assess clearance measured with quantitative polymerase chain reaction following dosing, and evaluate the pharmacodynamic effects on plasma methionine following a methionine loading study, providing a dietary model of HCU.

Synlogic has completed dosing of 30 total subjects over four cohorts which evaluated three different dose levels ($3x10^{11}$, $6x10^{11}$ and $1x10^{12}$ live cells)

and two different formulations at the $1x10^{12}$ dose. In each cohort, the subjects were randomly assigned to receive either SYNB1353 or a placebo (6 active/2 placebo per cohort). A methionine loading study was performed on day -1 and day 7 after an overnight fast, followed by a 24-hour collection period for the AUC assessments. Subjects were followed in the study for at least 28 days after the last dose.

At the $1x10^{12}$ dose, SYNB1353 decreased plasma methionine levels, as measured by the change in AUC from baseline, by -24.8% (95% CI -36.7,-10.6) and -26.2% (95% CI -39.0,-10.9) for the two different SYNB1353 formulations, compared to -2.1% (95% CI -15.7, 13.7) in the placebo group.

There were no serious adverse events (SAEs). One subject discontinued dosing due to an adverse event (AE). AEs were mild to moderate, transient and predominantly GI in nature. Frequency and severity of GI-related AEs were similar in the SYNB1353 and placebo groups (7 of 22 SYNB1353 compared to 3 of 8 placebo subjects had at least 1 GI-related AE). All subjects completing the 28-day analysis cleared SYNB1353 in feces.

Full results of the study will be presented at a future medical meeting.

Organizational Changes

To focus resources on advancing and optimizing the value of the Company's clinical stage and prioritized preclinical research programs, Synlogic has implemented a structural realignment, including a reduction in the Company's workforce by 25%, which is expected to extend its cash runway into the second half of 2024. The Company estimates that it will incur approximately $0.8 million of costs in connection with the reduction in workforce related to severance pay and other related termination benefits. The Company communicated the workforce reduction on November 30, 2022 and expects the majority of the costs associated with the reduction in force plan to be incurred during the fourth quarter ending December 31, 2022 and the first quarter ending March 31, 2023. The Company may also incur other material charges not currently contemplated due to events that may occur as a result of, or associated with, these actions.

Next Steps

Synlogic also confirmed the following anticipated milestones:

- Share proof of concept data for SYNB8802 for enteric hyperoxaluria in Q4 2022
- Initiate Phase 3 pivotal study of SYNB1934 for PKU in H1 2023

About Homocystinuria (HCU) & SYNB1353

HCU is a rare metabolic disease and inborn error of metabolism characterized by extreme levels of homocysteine and caused by an inherited deficiency in an enzyme known as cystathionine beta-synthase (CBS). When CBS is absent, homocysteine builds up in the blood and urine, putting patients at risk of multisystem complications, including acute thromboembolic events, optical damage from lens dislocation, skeletal deficiencies, and neurocognitive impairments. SYNB1353 is a novel, orally administered, non-systemically absorbed drug candidate designed to lower homocysteine levels in patients with HCU by consuming methionine, a precursor to homocysteine, in the gastrointestinal tract. It is the first drug candidate developed through a research collaboration between Synlogic and Ginkgo Bioworks and the first investigational medicine developed on Ginkgo's platform to enter the clinic. The U.S. Food and Drug Administration (FDA) granted Fast Track designation and Orphan Drug Designation (ODD) to SYNB1353 for the potential treatment of HCU. Synlogic holds worldwide development and commercialization rights to SYNB1353.

About Synlogic

Synlogic is a clinical-stage biotechnology company developing medicines through its proprietary approach to synthetic biology. Synlogic's pipeline includes its lead program in phenylketonuria (PKU), which has demonstrated proof of concept with plans to start a pivotal, Phase 3 study in the first half of 2023, and additional novel drug candidates designed to treat homocystinuria (HCU), enteric hyperoxaluria and gout. The rapid advancement of these potential biotherapeutics, called Synthetic Biotics, has been enabled by Synlogic's reproducible, target-specific drug design. Synlogic uses programmable, precision genetic engineering of well-characterized probiotics to exert localized activity for therapeutic benefit, with a focus on metabolic and immunological diseases. In addition to its clinical programs, Synlogic has a research collaboration with Roche on the discovery of a novel Synthetic Biotic for the treatment of inflammatory bowel disease or IBD. Synlogic has also developed two drug candidates through a research collaboration with Ginkgo Bioworks: SYNB1353, designed to consume methionine for the potential treatment of HCU, and SYNB2081, designed to lower uric acid for the potential treatment of gout. For additional information visit www.synlogictx.com.

Forward-Looking Statements

This press release contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, included in this press release regarding strategy, future operations, clinical development plans, future financial position, future revenue, projected expenses, prospects, plans and objectives of management are forward-looking statements. In addition, when or if used in this press release, the words "may," "could," "should," "anticipate," "believe," "look forward," "estimate," "expect," "intend," on track," "plan," "predict" and similar expressions and their variants, as they relate to Synlogic, may identify forward-looking statements. Examples of forward-looking statements, include, but are not limited to, statements regarding the potential of Synlogic's approach to Synthetic Biotics to develop therapeutics to address a wide range of diseases including: inborn errors of metabolism and inflammatory and immune disorders; our expectations about sufficiency of our existing cash balance; the future clinical development of Synthetic Biotics; the approach Synlogic is taking to discover and develop novel therapeutics using synthetic biology; and the expected timing of Synlogic's clinical trials of SYNB1618, SYNB1934, SYNB1353, SYNB8802 and SYNB2081 and availability of clinical trial data. Actual results could differ materially from those contained in any forward-looking statements as a result of various factors, including: the uncertainties inherent in the clinical and preclinical development process; the ability of Synlogic to protect its intellectual property rights; and legislative, regulatory, political and economic developments, as well as those risks identified under the heading "Risk Factors" in Synlogic's filings with the U.S. Securities and Exchange Commission. The forward-looking statements contained in this press release reflect Synlogic's current views with respect to future events. Synlogic anticipates that subsequent events and developments will cause its views to change. However, while Synlogic may elect to update these forward-looking statements in the future, Synlogic specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing Synlogic's view as of any date subsequent to the date hereof.

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