Synlogic Reports Positive Interim Phase 1/2a Data Demonstrating Safety, Tolerability and Proof-of-Mechanism in Healthy Volunteers for SYNB1618, in Development for the Management of Phenylketonuria (PKU)

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– Data demonstrate statistically significant dose-dependent effects on SYNB1618 activity-associated biomarkers, supporting further development of SYNB1618 –

– SYNB1618 dose established for treatment arm of ongoing Phase 1/2a study in patients with PKU; top-line data expected in mid-2019 –

– Company to hold conference call and webcast today, September 4, at 8:00 a.m. ET–

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 4, 2018-- Synlogic, Inc., (Nasdaq:SYBX) a clinical stage company applying synthetic biology to probiotics to develop novel, living medicines, today announced positive interim clinical data from the healthy volunteer (HV) arm of its ongoing Phase 1/2a study of SYNB1618 in HVs and patients with PKU. The first part of this trial, which evaluated SYNB1618 versus placebo (PBO) in single- (SAD) and multiple-ascending dose (MAD) cohorts of HVs, successfully met the study's primary objectives, to demonstrate safety and tolerability of SYNB1618 in HVs and to identify a suitable dose to evaluate in patients with PKU. Consistent with preclinical studies, the Phase 1/2a clinical data demonstrated that oral administration of SYNB1618 resulted in significant dose-dependent production of biomarkers specifically associated with SYNB1618 activity, demonstrating proof-of-mechanism.

"The significant dose-dependent production of SYNB1618-specific biomarkers in healthy volunteers is an exciting first step towards delivering a potential therapy for patients with PKU," said Aoife Brennan, M.B., B.Ch., Synlogic's interim president and chief executive officer and chief medical officer. "We have identified a dose for the next phase of our ongoing trial in patients with PKU and we look forward to expanding on these interim results when we report top-line data from the patient treatment arm of this trial in mid-2019. Importantly, the data also demonstrate the potential for our Synthetic Biotic platform to address conditions in which an engineered living medicine can be designed to perform a specific metabolic function within the gastrointestinal tract."

Synlogic's Synthetic Biotic platform leverages the tools and principles of synthetic biology to engineer a strain of probiotic bacteria (*E. coli* Nissle) to perform or deliver specific functions lost or damaged due to disease. SYNB1618, in development for the management of PKU, is designed to function in the gastrointestinal tract (GI) and has been engineered to consume phenylalanine (Phe), an essential amino acid that can accumulate to harmful levels in patients with PKU with severe consequences. SYNB1618 metabolizes Phe to harmless compounds including trans-cinnamic acid (TCA) in the blood which is further metabolized in the liver and excreted as hippurate (HA) in the urine. TCA and HA,therefore, represent specific biomarkers of SYNB1618 activity as demonstrated by Synlogic's preclinical data that were recently published in *Nature Biotechnology*.

Phase 1/2a Trial Design

Synlogic's Phase 1/2a trial is a randomized, double-blind, PBO-controlled study of orally administered SYNB1618, evaluating ascending doses administered on a single day and multiple ascending doses administered over seven days. The primary objective of the study was to assess safety and tolerability of SYNB1618 in HVs and to establish a suitable dose to evaluate in patients with PKU, with secondary objectives to characterize the microbial kinetics of SYNB1618 in feces, as measured by qPCR, and GI tolerability, assessed by GI-related adverse events. Exploratory endpoints were designed to evaluate the pharmacodynamic effects of SYNB1618, including previously identified biomarkers related to SYNB1618 activity, TCA in plasma and HA in urine.

In the SAD portion of this study, six cohorts of four HVs received a single dose of SYNB1618 ranging from $1x10^{10}$ to $5x10^{11}$ CFU or PBO (3 treated:1 PBO). In the MAD portion of this study, four cohorts of eight HVs received either SYNB1618 at doses of up to $1x10^{11}$ CFU TID or PBO (6 treated:2 PBO), for seven days. During the treatment part of the study, subjects were housed in a clinical unit and provided a defined diet. The activity of SYNB1618 was evaluated in fasted subjects in both the SAD and MAD cohorts after administration of a standardized breakfast drink containing a defined amount of protein. At one dose level in the SAD portion of the study, solid food containing an equivalent amount of protein was substituted for the liquid meal. In addition, a labeled Phe tracer (D5-Phe) was orally administered. Blood and urine were collected over a subsequent six-hour period and several metabolites were measured including Phe and SYNB1618-specific biomarkers of Phe metabolism, TCA in blood and HA in urine. This was conducted in the SAD cohorts on the day of dosing and in the MAD cohorts on Day -1 (baseline) and Day 7 (the last day of dosing).

SAD Phase 1 Results:

In the SAD portion of this study, which included a total of 24 subjects, the maximum tolerated dose (MTD) was 2×10^{11} CFU. There were no drug-related significant adverse events (SAEs) reported. All AEs were mild-to-moderate in severity; of the moderately severe AEs, nausea and vomiting were the most common. A statistically significant dose-dependent increase in both plasma TCA and urinary HA was observed in SYNB1618 treated subjects but not in those treated with PBO. Production of metabolites from Phe administered as a free amino acid was similar to Phe administered as whole protein. In addition, production of metabolites was similar whether the protein was administered as a liquid or as a solid meal.

MAD Phase 1 Results:

In the MAD portion of this study, which included a total of 32 subjects, HV were administered PBO or SYNB1618 at doses of up to $1x10^{11}$ CFU TID for seven days. No drug-related SAEs were reported. All AEs were mild to moderate and observed in both the SYNB1618-treated and PBO groups. Of the moderately severe AEs, nausea and vomiting were the most common; only one subject in the highest dose cohort discontinued dosing. As observed in the SAD portion of the study, a statistically significant dose-dependent increase in plasma TCA and urinary HA was observed in SYNB1618-treated subjects but not in those treated with PBO. In HVs, who all have normal Phe metabolism, there was no impact on blood Phe levels. All HVs enrolled in the study have cleared SYNB1618 from their GI tracts.

SYNB1618 Clinical Development Plans and Upcoming Milestones

Synlogic's ongoing Phase 1/2a trial of SYNB1618 will advance in patients with PKU, who will be administered $7x10^{10}$ CFU of SYNB1618. Synlogic expects to report top-line data from the patient treatment arm of this study in mid-2019 and plans to present final data from this clinical trial, including data from both HVs and patients, at an appropriate medical meeting. More information about Synlogic's Phase 1/2a clinical trial in healthy adult volunteers and patients with PKU can be found at https://clinicaltrials.gov under the study ID NCT03516487. In addition, Synlogic will continue to optimize manufacturing process development and formulation of SYNB1618 in preparation for later stage clinical studies.

Conference Call & Webcast Information

Synlogic will host a conference call and live webcast at 8:00 a.m. ET on Tuesday, September 4, 2018. To access the live webcast, please visit the "Event Calendar" page within the Investors and Media section of the Synlogic website at https://investor.synlogictx.com/. Alternatively, investors may listen to the call by dialing +1 (844) 815-2882 from locations in the United States or +1 (213) 660-0926 from outside the United States. The conference ID number is 1584778. A replay of the call will be available for seven days post the event, investors may listen to the call by dialing +1 (855) 859-2056 from locations in the United States or +1 (404) 537-3406 from outside the United States. A replay of the webcast will be available on the Synlogic website for 90 days following the call.

About Phenylketonuria (PKU)

PKU is caused by a defect in the gene encoding phenylalanine hydroxylase (PAH), a liver enzyme that metabolizes Phe. Phe is an essential amino acid that enters the body as a component of dietary protein and can be toxic if it accumulates in the blood and brain. Current disease management of PKU involves strict dietary protein restriction with the consumption of Phe-free protein supplements. Life-long Phe control is challenging due to the highly restrictive nature of the diet and patients typically experience worsening neurological function depending on the severity of their genetic mutation and their treatment compliance. PKU is diagnosed at birth, and the National PKU Alliance estimates that there are currently approximately 16,500 people living with the disorder in the U.S.

About Synlogic

Synlogic is pioneering the development of a novel class of living medicines, Synthetic Biotic medicines, based on its proprietary drug development platform. Synlogic leverages the tools and principles of synthetic biology to genetically engineer probiotic microbes to perform or deliver critical functions missing or damaged due to disease. The company's two lead programs, SYNB1020 and SYNB1618, target hyperammonemia as a result of liver damage or genetic disease, and PKU, respectively. When delivered orally, Synthetic Biotic medicines can act from the gut to compensate for the dysfunctional metabolic pathway and have a systemic effect, with the potential to significantly improve symptoms of disease for affected patients. In addition, the company is leveraging the broad potential of its platform to create Synthetic Biotic medicines for the treatment of more common diseases, including liver disease, inflammatory and immune disorders, and cancer. Synlogic is collaborating with AbbVie to develop Synthetic Biotic-based treatments for inflammatory bowel disease (IBD). For more information, please 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, including statements regarding Synlogic's plans and expectations for the development of SYNB1618. All statements, other than statements of historical facts, included in this press release regarding strategy, future operations, 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," "estimate," "expect," "intend," "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 platform to develop therapeutics to address a wide range of diseases including: cancer, inborn errors of metabolism, liver disease, and inflammatory and immune disorders; the future clinical development of Synthetic Biotic medicines; the approach Synlogic is taking to discover and develop novel therapeutics using synthetic biology; and the expected timing of Synlogic's clinical trials and availability of clinical trial data. Actual results could differ materially from those contained in any forward-looking statement as a result of various factors, including: the uncertainties inherent in the 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 SEC. 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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