June 17, 2015

Synergy Pharmaceuticals Announces Positive Results in the First Phase 3 Trial of Plecanatide in Patients with Chronic Idiopathic Constipation (CIC)

NEW YORK-- Synergy Pharmaceuticals Inc. (NASDAQ:SGYP) today announced positive top-line results from the first of two pivotal phase 3 clinical trials evaluating the efficacy and safety of two different plecanatide treatment doses (3.0 mg and 6.0 mg), taken as a tablet once-a-day, in 1,346 adult patients with chronic idiopathic constipation (CIC).

Preliminary analysis of the data indicates that both plecanatide 3.0 mg and 6.0 mg doses met the study's primary endpoint and demonstrated statistical significance in the proportion of patients in the intention-to-treat population who were durable overall responders compared to placebo during the 12-week treatment period (21.0% in 3.0 mg and 19.5% in 6.0 mg dose groups compared to 10.2% in placebo; $p<0.001$ for both doses). The durable overall responder endpoint is the current FDA endpoint required for US approval in CIC. Plecanatide would be the first drug approved for CIC using the more stringent regulatory requirement for durability in the response. Notably, plecanatide was safe and well tolerated at both doses; the most common adverse event was diarrhea, which occurred in 5.9% of patients in 3.0 mg and 5.5% of patients in 6.0 mg dose groups compared to 1.3% of placebo-treated patients.

"We are very pleased with these results and how well they confirm earlier plecanatide data observed in the phase 2b/3 trial," said Gary S. Jacob, Ph.D., Chairman and CEO of Synergy. "These results strengthen our belief that plecanatide has the potential to not only effectively treat constipation but with a durability and tolerability profile that is ideal for chronic use. We look forward to the results of our second pivotal trial in the coming weeks."

Stool consistency was the key secondary endpoint reported with top-line analyses; both 3.0 mg and 6.0 mg plecanatide doses showed statistically significant improvement from baseline in Bristol Stool Form Scale (BSFS) scores compared to placebo (mean increase of 1.53 in 3.0 mg and 1.52 in 6.0 mg dose groups compared to a mean increase of 0.77 in placebo; $p<0.001$ for both doses). The observed improvements began at Week 1, continued throughout the 12-week treatment period, and returned towards baseline with no indication of an exaggerated or rebound effect following discontinuation of treatment.

15 patients in the trial (1.1%) experienced serious adverse events but there was no imbalance across treatment groups in either incidences or individual serious adverse events. Overall, the rates of withdrawal from treatment because of an adverse event were

low (5.1 % in 3.0 mg and 5.0% in 6.0 mg dose groups compared to 1.3% in placebo) and discontinuations due to diarrhea were infrequent (2.7% in 3.0 mg and 2.4% in 6.0 mg dose groups compared to 0.4% in placebo).

No clinically relevant abnormalities were observed in serum chemistries, hematology, urinalysis, ECG or vital signs measurements.

Synergy plans to announce top-line data results from the second phase 3 CIC trial with plecanatide in the first half of 3Q 2015. The company plans to file its first new drug application (NDA) with plecanatide in the CIC indication in the fourth quarter of this year.

The Plecanatide Phase 3 CIC Program

Design

The plecanatide phase 3 CIC program includes two randomized, 12-week, double-blind, placebo-controlled pivotal trials evaluating the efficacy and safety of two different plecanatide treatment doses (3.0 mg and 6.0 mg), taken as a tablet once-a-day, in patients with CIC. Both trials include a two-week pre-treatment baseline period, a 12-week treatment period, and a two-week post-treatment period. The phase 3 CIC program was designed to support regulatory submission in the U.S.

The first phase 3 CIC trial was conducted in North America and assessed 1,346 adult patients (19.2% males and 80.8% females) that were randomly assigned to take 3.0 mg or 6.0 mg plecanatide or placebo once-a-day during the 12 week treatment period (453 patients in the 3 mg dose group, 441 patients in the 6.0 mg dose group and 452 patients in the placebo group).

Primary Endpoint

The primary endpoint for both trials is the proportion of durable overall responders (%), which is the current regulatory endpoint required for U.S. approval in CIC. The FDA has defined a durable overall responder as a patient who fulfills both ≥ 3 complete spontaneous bowel movements (CSBMs) per week plus an increase of ≥ 1 CSBM from baseline in the same week, for 9 out of the 12 treatment weeks. In addition, the same patient must be an overall responder for at least 3 of the last 4 treatment weeks in order to be considered a *durable* overall responder.

Patient Population

Patients were selected using Rome 3 criteria modified for CIC and had (1) fewer than 3 defecations per week, (2) loose stools occurring rarely without laxatives, (3) inadequate criteria for irritable bowel syndrome with constipation (IBS-C), and (4) at least two of the following applied to at least 25% of defecations: (a) straining during evacuation, (b) lumpy or hard stools, (c) sensation of anorectal obstruction or blockage. Rome 3 requires patients to fulfill the criteria for the last 3 months with symptom onset at least 6 months prior to diagnosis.

About Plecanatide

Plecanatide is Synergy's lead uroguanylin analogue in pivotal phase 3 clinical development to treat patients with CIC and IBS-C. Uroguanylin is a naturally occurring gastrointestinal (GI) peptide produced by humans in the small intestine and plays a key role in regulating normal GI activity. Orally administered plecanatide is designed to mimic uroguanylin's natural activity and regulate the movement of fluid required for normal digestion.

About Synergy Pharmaceuticals Inc.

Synergy Pharmaceuticals (NASDAQ:SGYP) is a biopharmaceutical company focused on the development of novel therapies to treat GI diseases and disorders. Synergy's proprietary platform of uroguanylin analogues includes two late-stage clinical assets, plecanatide and dolcanatide (SP-333). Dolcanatide has successfully completed a phase 2 study in patients with opioid-induced constipation and is currently being evaluated for the treatment of ulcerative colitis. For more information, please visit www.synergypharma.com.

Forward-Looking Statements

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward- looking words such as "anticipate," "planned," "believe," "forecast," "estimated," "expected," and "intend," among others. These forward-looking statements are based on Synergy's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, substantial competition; our ability to continue as a going concern; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payer reimbursement; limited sales and marketing efforts and dependence upon third parties; and risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. There are no guarantees that future clinical trials discussed in this press release will be completed or successful or that any product will receive regulatory approval for any indication or prove to be commercially successful. Investors should read the risk factors set forth in Synergy's Form 10-K for the year ended December 31, 2014 and other periodic reports filed with the Securities and Exchange Commission. While the list of factors presented here is considered representative, no such list should be considered to be a complete statement of all potential risks and uncertainties. Unlisted factors may present significant additional obstacles to the realization of forward-looking statements. Forward-looking statements included herein are made as of the date hereof, and Synergy does not undertake any obligation to update publicly such statements to reflect subsequent events or circumstances.

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