**Synergy Pharmaceuticals Highlights New Data at Digestive Disease Week (DDW) 2018 Linking Uroguanylin Deficiency to Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome with Constipation (IBS-C)**

NEW YORK--(BUSINESS WIRE)-- Synergy Pharmaceuticals Inc. (NASDAQ:SGYP), a biopharmaceutical company focused on the development and commercialization of novel gastrointestinal (GI) therapies, announced today new data presented at Digestive Disease Week (DDW) 2018 showing chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) are associated with depressed levels of uroguanylin, a naturally occurring and endogenous human GI peptide.

“The discovery of uroguanylin deficiency in CIC and IBS-C patients represents a historic advance towards better understanding and treating these two complex GI disorders,” said Scott A. Waldman, M.D., PhD, Professor and Chair, Pharmacology & Experimental Therapeutics, Sidney Kimmel Medical College, Thomas Jefferson University. “This is the first study to measure circulating uroguanylin responses in humans, and we observed a significant correlation between chronic constipation and depressed levels of uroguanylin following food intake. These findings suggest that chronic constipation syndromes may, in part, reflect an insufficiency of uroguanylin. In turn, this peptide insufficiency can be corrected, and the pathophysiology underlying chronic constipation reversed, by administering oral uroguanylin analogs such as plecanatide.”

“This is an exciting day for Synergy and for the broader GI community,” said Patrick H. Griffin, M.D., Chief Medical Officer at Synergy Pharmaceuticals Inc. “For more than a decade, Synergy has been committed to advancing the understanding of uroguanylin and the role this key peptide plays in human GI physiology. This discovery provides novel insight into the complex biology of CIC and IBS-C and reinforces our belief that the best approach to reversing this uroguanylin deficiency is by administering oral analogs of uroguanylin. This is the foundation of Synergy’s approach and why we see significant potential for our uroguanylin analog platform to transform the treatment paradigm and benefit patients suffering from GI conditions.”

**Study Results**

The objective of the study was to evaluate and compare pre- and postprandial circulating...
pro-uroguanylin levels in healthy subjects versus patients with CIC or IBS-C. The study included 60 healthy subjects and 107 patients with CIC or IBS-C who participated in an overnight fast, followed by a standardized meal of 750 calories. Pro-uroguanylin and uroguanylin levels were measured at fasting and then at 30, 60 and 90 minutes following the meal.

Results showed that pro-uroguanylin concentrations were lower in patients at fasting and at each time point following the meal compared to healthy subjects (difference in mean pro-uroguanylin concentrations was 583 pg/mL, 95% CI: 405, 761; p<0.0001). Mean pro-uroguanylin plasma concentrations were consistently >30% lower in patients than in healthy subjects. Similarly, patients also had lower circulating uroguanylin levels at preprandial and all postprandial time points (the difference in mean uroguanylin concentration was 112 pg/mL, 95% CI: 74, 150; p<0.0001).

These results suggest a novel pathophysiological hypothesis in which chronic constipation may reflect a paracrine hormone insufficiency of pro-uroguanylin in the small intestine. The correlative therapeutic hypothesis suggests that this pathophysiology can be reversed by oral supplementation with a uroguanylin analog such as plecanatide.

**Indications and Usage**

TRULANCE (plecanatide) 3 mg tablets is indicated in adults for the treatment of Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome with Constipation (IBS-C).

**IMPORTANT SAFETY INFORMATION**

**WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS**

TRULANCE® is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile mice administration of a single oral dose of plecanatide caused deaths due to dehydration. Use of TRULANCE should be avoided in patients 6 years to less than 18 years of age. The safety and efficacy of TRULANCE have not been established in pediatric patients less than 18 years of age.

**Contraindications**

- TRULANCE is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- TRULANCE is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

**Warnings and Precautions**

**Risk of Serious Dehydration in Pediatric Patients**

- TRULANCE is contraindicated in patients less than 6 years of age. The safety and effectiveness of TRULANCE in patients less than 18 years of age have not been established. In young juvenile mice (human age equivalent of approximately 1 month to less than 2 years), plecanatide increased fluid secretion as a consequence of
stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than older patients to develop severe diarrhea and its potentially serious consequences.

- Use of TRULANCE should be avoided in patients 6 years to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in young mice and the lack of clinical safety and efficacy data in pediatric patients, use of TRULANCE should be avoided in patients 6 years to less than 18 years of age.

**Diarrhea**

- Diarrhea was the most common adverse reaction in the four placebo-controlled clinical trials for CIC and IBS-C. Severe diarrhea was reported in 0.6% of TRULANCE-treated CIC patients, and in 1% of TRULANCE-treated IBS-C patients.

- If severe diarrhea occurs, the health care provider should suspend dosing and rehydrate the patient.

**Adverse Reactions**

- In the two combined CIC clinical trials, the most common adverse reaction in TRULANCE-treated patients (incidence ≥2% and greater than in the placebo group) was diarrhea (5% vs 1% placebo).

- In the two combined IBS-C clinical trials, the most common adverse reaction in TRULANCE-treated patients (incidence ≥2% and greater than in the placebo group) was diarrhea (4.3% vs 1% placebo).

Please also see the full Prescribing Information, including Box Warning, for additional risk information.

**About Chronic Idiopathic Constipation (CIC)**

CIC affects approximately 14 percent of the global population, disproportionately affecting women and older adults. People with CIC have persistent symptoms of difficult-to-pass and infrequent bowel movements. In addition to physical symptoms including abdominal bloating and discomfort, CIC can adversely affect an individual’s quality of life, including increasing stress levels and anxiety.

**About Irritable Bowel Syndrome with Constipation (IBS-C)**

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by recurrent abdominal pain and associated with two or more of the following: related to defecation, associated with a change in the frequency of stool, or associated with a change in the form (appearance) of the stool. IBS can be subtyped by the predominant stool form: constipation (IBS-C), diarrhea (IBS-D) or mixed (IBS-M). Those within the IBS-C subtype experience hard or lumpy stools more than 25 percent of the time they defecate, and loose or watery stools less than 25 percent of the time. It is estimated that the prevalence of IBS-C in the U.S. adult population is approximately 4 to 5 percent.
About TRULANCE®

TRULANCE® (plecanatide) is a once-daily tablet approved for adults with CIC or IBS-C. With the exception of a single amino acid substitution for greater binding affinity, TRULANCE is structurally identical to uroguanylin, a naturally occurring and endogenous human GI peptide. Uroguanylin activates GC-C receptors in a pH-sensitive manner primarily in the small intestine, stimulating fluid secretion and maintaining stool consistency necessary for regular bowel function.

About Synergy Pharmaceuticals Inc.

Synergy is a biopharmaceutical company focused on the development and commercialization of novel GI therapies. The company has pioneered discovery, research and development efforts on analogs of uroguanylin, a naturally occurring and endogenous human GI peptide, for the treatment of GI diseases and disorders. Synergy’s proprietary GI platform includes one commercial product TRULANCE® (plecanatide) and a second product candidate, dolcanatide. For more information, please visit www.synergypharma.com.

Forward-Looking Statement

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 Annual Report on Form 10-K for the year ended December 31, 2017 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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