WHAT IS PLECANATIDE?

Plecanatide is a promising investigational drug being developed by Synergy Pharmaceuticals Inc. for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C), among the most common gastrointestinal (GI) disorders in the United States and the world. Plecanatide is a member of a new class of essentially non-systemic oral drugs known as guanylate cyclase-C (GC-C) agonists.

HOW DOES PLECANATIDE RELIEVE CIC?

Plecanatide is a synthetic analog of uroguanylin, a natural human peptide hormone that regulates ion and fluid transport in the GI tract. Uroguanylin binds to and activates GC-C receptors on mucosal epithelial cells lining the GI tract. Activation of these receptors triggers an increase in a key intracellular mediator called cyclic guanosine monophosphate (cGMP), which induces fluid secretion into the intestinal lumen necessary for normal bowel movements. Increased cGMP has also been reported to have other physiologic benefits related to abdominal discomfort, pain and bloating.

Preclinical studies suggest that orally-administered plecanatide mimics the function of uroguanylin, acting locally in the proximal intestine to stimulate secretion of fluid into the lumen, facilitating bowel movements and ameliorating GI inflammation.1,2,3

FACT:

Plecanatide is a member of a novel class of oral drugs known as guanylate cyclase-C (GC-C) agonists.

In a large multicenter clinical trial in patients with chronic idiopathic constipation (CIC), plecanatide was well tolerated, and met the primary and key secondary endpoints.
WHAT WAS THE PURPOSE OF THE 2012 PLECANATIDE CIC CLINICAL TRIAL?

The official title of the Plecanatide CIC Study is:

Study SP304-20210: A Randomized, 12-Week, Double-Blind, Placebo-Controlled, Repeat-Dose, Oral, Dose-Ranging Study to Assess the Safety and Efficacy of Plecanatide in Patients With Chronic Idiopathic Constipation (ClinicalTrials.gov Identifier: NCT01429987).4

The study was designed to evaluate whether plecanatide could increase the number of complete spontaneous bowel movements (CSBMs), as well as benefit other bowel measures associated with the constipated state such as stool straining and consistency, along with general quality of life, in people with CIC.

WHO PARTICIPATED IN THE PLECANATIDE CIC STUDY?

Participants were enrolled at 113 clinical sites in the United States, and included 951 men and women between the ages of 18 and 75 years. All participants had CIC and fewer than 3 CSBMs per week at baseline.

WHAT WAS THE CLINICAL STUDY DESIGN?

Study participants were randomized to four study arms to determine the efficacy and safety of 3 doses of plecanatide (0.3, 1.0, 3.0 mg), compared to placebo, over the course of the 12-week dosing regimen. The primary outcome measure was the frequency of CSBMs, and participants were required to call in daily to report their bowel movement data. Participants also reported on secondary outcome measures, including straining and abdominal symptoms, stool consistency, and time to first bowel movement.

HOW EFFECTIVE IS PLECANATIDE AT TREATING CIC?

All doses of plecanatide demonstrated statistically significant improvement from baseline in the number of CSBMs (versus placebo). The greatest improvement in CSBM was observed at the 3 mg plecanatide dose. Over the course of the

FACT:
The 3 mg plecanatide dose appeared to be safe, well tolerated, and effective for the treatment of CIC.

Participants reported an increase in complete spontaneous bowel movements (CSBMs), as well as decreases in straining, stool hardness, and time to first bowel movement.
12-week study, 19% of participants treated daily with 3 mg plecanatide were durable* responders (vs. 10.7% for placebo; p<0.01). More than half of patients dosed at 3 mg plecanatide treatment experienced an increase of at least one CSBM per week relative to baseline (52.3% vs. 36.8% for placebo; p<0.001). Statistically significant improvements were also seen in other key secondary endpoints, including stool consistency, straining, and time to first spontaneous bowel movement (3 mg plecanatide vs. placebo; p<0.001). Increasing efficacy was observed at increasing dose levels. In addition, responders to treatment reported statistically significant improvements in constipation-associated symptoms and quality of life (measured by Patient Assessment of Constipation (PAC) Symptoms (SYM) and Quality of Life (QOL) questionnaires).

**HOW SAFE IS PLECANATIDE?**

All doses of plecanatide appeared to be safe and well tolerated. There were no serious adverse events attributed to study treatment. The most common adverse event reported was diarrhea (9.7% at 3 mg plecanatide vs. 1.3% placebo). Notably, study withdrawal due to diarrhea was infrequent (3% at 3 mg plecanatide vs. 0.4% for placebo). Of the 237 patients treated at the 3 mg dose, only 23 patients experienced diarrhea. All but one case of diarrhea were mild or moderate in severity. The safety data from this large multicenter trial are consistent with data generated in the Phase I and Phase IIa clinical trials of plecanatide.5,6

**WHEN WAS THE STUDY COMPLETED, AND WHEN WILL THE FULL DATA SET BE RELEASED?**

The study was completed in late 2012. Synergy is continuing to analyze the data and assembling the clinical study report for submission to the FDA. The first presentation of scientific results from the study occurred at Digestive Disease Week® 2013.7 Further data will also be presented at other upcoming major scientific meetings in 2013.

*Durable responder is defined as: a responder in at least 9 of 12 weeks of study, and a responder in at least 3 of the last 4 weeks of treatment.
REFERENCES:
1. Brancale A, Jacob GS, Shailubhai K. Plecanatide, a Superior Analog of Uroguanylin, as an Oral Drug Candidate for Treatment of Gastrointestinal Functional Disorders and Diseases. Poster presentation at: Joint International Neurogastroenterology and Motility Meeting; September 2012; Bologna, Italy.

Digestive Disease Week (DDW®) is the largest international gathering of physicians, researchers and academics in the fields of gastroenterology, hepatology, endoscopy and gastrointestinal surgery. Jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy (ASGE) and the Society for Surgery of the Alimentary Tract (SSAT), DDW takes place May 18 – 21, 2013, at the Orange County Convention Center, Orlando, FL. The meeting showcases more than 5,000 abstracts and hundreds of lectures on the latest advances in GI research, medicine and technology. More information can be found at www.ddw.org.