WHAT IS PLECANATIDE?
Plecanatide is a promising investigational drug being developed by Synergy Pharmaceuticals 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. Preclinical and clinical studies suggest that plecanatide has the potential to address the significant unmet medical needs of millions of patients suffering with CIC and IBS-C.

WHY IS PLECANATIDE NOVEL?
Plecanatide is different from most other drugs used to treat GI disorders and diseases. Plecanatide is a member of a new class of essentially non-systemic oral drugs known as guanylate cyclase-C (GC-C) agonists. By acting locally in the proximal intestine, plecanatide promotes intestinal fluid secretion needed for normal bowel function and reduces the abdominal symptoms that are often associated with GI disorders.

HOW DOES PLECANATIDE RELIEVE CIC AND IBS-C?
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

FACT:
Synergy is developing plecanatide for the treatment of patients suffering from chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C).

Plecanatide is a member of a novel class of oral drugs known as guanylate cyclase-C (GC-C) agonists and mimics the function of the natural human peptide hormone, uroguanylin.
lumen necessary for normal bowel movements. Increased cGMP has also been reported to have other physiologic benefits related to abdominal discomfort, pain and bloating.

*In vitro* binding studies establish that plecanatide binds to the same GC-C receptors in the human proximal intestine as uroguanylin. 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, thereby facilitating bowel movements and ameliorating GI inflammation.\(^2,3,4\)

Plecanatide is identical to uroguanylin except for the substitution of a single amino acid, resulting in a molecule that is eight times more potent than the natural hormone.\(^5\)

IN WHAT STAGE OF DEVELOPMENT IS PLECANATIDE?
Synergy completed a large multicenter trial of plecanatide for the treatment of CIC in December 2012, and announced in January, 2013 that the drug was well tolerated and met the primary and key secondary endpoints of the clinical study. 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 will be at Digestive Disease Week\(^5\) 2013.\(^6\)

Synergy initiated a Phase IIb study of plecanatide for the treatment of IBS-C in December 2012.\(^7\) This randomized, 12-week, double blind, placebo-controlled, dose-ranging study of 350 patients is expected to be completed in early 2014.

WHAT WERE THE DESIGN AND RESULTS OF THE PLECANATIDE CIC STUDY?
The large, multicenter, randomized, double blind, placebo-controlled, repeat oral dose, dose-ranging, CIC 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 consistency and straining, along with general quality of life, in people with CIC. The 12-week study included 951 patients with CIC, enrolled at 113 clinical sites across the U.S.6

All doses of plecanatide studied in this trial (0.3, 1.0, and 3.0 mg) showed statistically significant increases in the number of CSBMs reported by patients (compared to placebo). Statistically significant improvements were also seen in key secondary endpoints, including stool consistency, straining, and time to first spontaneous bowel movement. Increasing efficacy was observed at increasing dose levels with the greatest improvements at the 3 mg dose. Over the course of the 12-week study, 19% of participants treated daily with 3 mg plecanatide were durable* responders (vs. 10.7% for placebo; p<0.01); and 52% of patients had an improvement of at least 1 CSBM per week over the course of treatment.6

**HOW SAFE IS PLECANATIDE?**

In the large multicenter trial, all doses of plecanatide studied 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). All but one case of diarrhea was mild or moderate in severity.6

**WHAT MAKES PLECANATIDE SO PROMISING?**

Plecanatide is a novel peptide designed to mimic the function of a natural human peptide hormone to regulate fluid secretion in the GI tract. Preclinical and

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*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.
clinical data suggest that plecanatide has the potential to treat chronic constipation (and possibly other bowel disorders) without inducing significant diarrhea. The efficacy and safety of plecanatide for the treatment of CIC are supported by a large multicenter trial, which included 951 participants with CIC. These data are consistent with the findings in a Phase IIa trial in CIC patients and a Phase I study in healthy volunteers.

REFERENCES:

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