CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA CONSULT TRACKING NUMBER	AT 2016-046
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DATE OF CONSULT REQUEST	March 1, 2016
REVIEW DIVISION	Division of Gastroenterology and Inborn Errors Products (DGIEP)
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REVIEW COMPLETION DATE	December 5, 2016
ESTABLISHED NAME/TRADE NAME	Plecanatide/SP-304
APPLICANT	Synergy
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Stool frequency, stool consistency, and straining
COA NAME(S)	Single PRO sign/symptom items
INDICATION	Treatment of chronic idiopathic constipation (CIC) in adult patients
INTENDED POPULATION(S)	Adult patients (18 and 80 years of age, inclusive) meeting the Rome III functional constipation criteria as modified for this study for at least 3 months prior to the Screening visit
PLEASE CHECK ALL THAT APPLY:	☐Rare Disease/Orphan Designation ☐Pediatric

In animals, plecanatide was rapidly absorbed following oral administration, but it did not persist in the plasma since it does not bind to plasma proteins. Plecanatide did not accumulate in plasma with repeated oral dosing and there were no clear sex differences in plecanatide exposure. Plecanatide and its active metabolite SP-338 did not interact with key transporters or CYP metabolic enzymes in the GI tract. Despite systemic exposure in animal studies, results from general, reproductive, and developmental toxicity studies with plecanatide demonstrated substantial safety margins compared to the MRHD. Plecanatide was not genotoxic in vitro or in vivo and was not carcinogenic in rats or mice.

Toxicity studies in juvenile mice suggested that very young mice, less than postnatal day 21, exhibit increased sensitivity to plecanatide compared to older juvenile mice, with ages corresponding to approximately 2 years of age in humans. Overall, the nonclinical safety data support the approval of plecanatide for the treatment of CIC at (b) (4) mg/day in adults.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Plecanatide is a synthetic analogue of human endogenous peptide uroguanylin and is an agonist of the guanylate cyclase- C (GC-C) receptor. GC-C receptors are found in the GI tract and are involved in the regulation of fluid and electrolyte transport. Binding of an agonist to the GC-C stimulates cyclic guanosine monophosphate (cGMP) synthesis and activates the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), a major chloride channel in the GI tract. The result is chloride and sodium/potassium ion efflux and secretion of fluid into the intestinal lumen. This fluid secretion is expected to facilitate bowel movements.

4.5.2. Pharmacodynamics

In pharmacodynamic (PD), in vitro screening studies, plecanatide did not exhibit any off-target binding or activity at a large number of targets, including G-protein coupled and neurotransmitter receptors, ion channels, or cytochrome P450 metabolic enzymes. These data suggest that plecanatide is unlikely to produce any potential adverse off-target effects in vivo at clinically relevant doses.

The sponsor submitted a Request for a Waiver of TQT Evaluation on May 16, 2014. In an FDA Advice Letter dated August 7, 2014, the FDA agreed that there was no need for Synergy to conduct a TQT study because at the plecanatide 3 or 6 mg QD doses, the maximum total plasma concentration was expected to be too low for the quantification of both plecanatide and the SP-338
metabolite.

In phase 1 study SP304101-08, PD analyses were based on the frequency and consistency of BMs. Overall, mean time to first stool post-dose was variable across the dose range. Nonetheless, there was a trend toward lower mean time to first stool values with higher doses of plecanatide. Mean stool consistency increased on the BSFS (i.e., indicating looser stools) following administration of single doses of plecanatide compared to 7 days pre-dose. Patients with an increase in BMs post-baseline had looser stools following plecanatide administration compared to placebo, which demonstrated a positive PD effect with respect to the potential for plecanatide as a treatment for constipation. These results were repeated in the phase 2 and 3 studies.

4.5.3. Pharmacokinetics

The PK program included evaluations of the transmembrane permeability of plecanatide and SP-338, plecanatide' s biologically active metabolite/ (b) (4) product, across Caco-2 cell monolayers and as substrates or inhibitors of the efflux transporters human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in these cells . Neither plecanatide nor SP-338 was a substrate or a significant inhibitor of P-gp or BCRP under the conditions of these studies.

The clinical PK of plecanatide was evaluated in multiple phase 1 and 2 studies. In Study SP304101-08, patients in each dose cohort received a single oral dose (0.1, 0.3, 0.9, 2.7, 5.4, 8.1, 16.2, 24.3, or 48.6 mg) of plecanatide solution or placebo solution under fasted conditions. No measurable concentrations of plecanatide were observed in plasma samples collected during the course of this study up to 48 hours post-dose. Likewise, in phase 2a, 2b, and 3 studies SP304201-09, SP304-20210, and SP304203-03 no measurable concentrations of plecanatide or SP-338 were observed in plasma samples collected during the course.

Plecanatide and SP-338 were also evaluated as inhibitors of CYP2C9 and CYP3A in human liver microsomes and as inducers of CYP3A in intact fresh human hepatocytes. The CYP

enzymes 2C9 (inhibition experiments) and 3A (inhibition and induction experiments) were studied because these CYP enzymes are predominant in the intestine and there is limited systemic exposure to plecanatide following oral dosing. Results indicated that neither plecanatide nor SP-338 is an inhibitor of CYP3A or CYP2C9, or an inducer of CYP3A in vitro

Please see the Clinical Pharmacology review by Dilara Jappar, PhD for more details.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable