CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208745Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**208-745**
Relevant IND(s)	**74883**
Submission Date (s)	**01/29/2016, 9/22/2016**
PDUFA Date:	**01/29/2017**
Brand Name	**TRULANCE™**
Generic Name	**Plecanatide**
Submission Type	**Original, 505(b)(1), NME**
Dosage Form, Strength	**Tablet, 3 mg**
Proposed indication	**Treatment of chronic idiopathic constipation (CIC) in adults**
Sponsor Recommended Dosing Regimen	**3 mg Once daily**
Sponsor	**Synergy Pharmaceuticals Inc**
OND Division	**Division of Gastroenterology and Inborn Errors Products**
OCP Division	**Division of Clinical Pharmacology 3**
OCP Reviewer	**Dilara Jappar, Ph.D.**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**

Table of Contents

1. Executive Summary

Plecanatide (SP-304) is a synthetic, 16-amino acid peptide with 2 disulfide bonds that is a second-in-class guanylate cyclase-C (GC-C) receptor agonist. The proposed indication for plecanatide is treatment of chronic idiopathic constipation in adults with 3 mg oral dose once daily. In support of this NDA, the sponsor had submitted 7 *in-vitro* studies to evaluate the potential drug-drug interaction, 2 phase I studies to evaluate the food effect and single ascending dose PK in healthy subjects, 3 phase II studies, 2 phase III efficacy and safety studies with 3 mg and 6 mg dose and one long-term phase III safety study to support the safety and efficacy of plecanatide. In addition, the submission contained 4 bioanalytical validation reports. PK samples were also obtained from the patient population in the phase 2 and 3 studies.

1.1 Recommendations

The Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling languages is reached between the FDA and the sponsor.

1.2 Recommended Post-Marketing Studies

None

1.3 Clinical Pharmacology Highlights

Dose-Response for Efficacy*:*
Exposure-response relationship other than dose response for efficacy for plecanatide was not evaluated since plecanatide did not have measurable systemic exposure.
Phase 2b study (SP304-20210) had evaluated 0.3, 1.0, and 3.0 mg QD oral doses of plecanatide versus placebo in a total of 951 CIC patients over a 12-week treatment period. The 3.0 mg dose provided the highest overall responder rate (19.0% vs. 10.7% for placebo) and a statistically significant treatment difference compared to placebo ($p = 0.009$) while 1 mg dose did not result in statistically significant difference from the placebo ($p = 0.057$). Interestingly, 0.3 mg dose level also resulted in a statistically significant difference from the placebo ($p = 0.016$) although the sponsor claims that 0.3 mg dose was examined in an exploratory nature.
Two dose levels, 3 mg and 6 mg, were evaluated in 2 phase III studies in CIC patients with 12 weeks treatment period. No dose-response was observed between 3 mg and 6 mg doses for primary efficacy endpoint while both dose levels have shown statistically significant improvement over placebo.

Dose-Response for Safety:
Exposure-response relationship other than dose-response for safety for plecanatide was not evaluated since plecanatide did not have measurable systemic exposure.
In the phase 2a study (SP304201-09) with 0.3, 1.0, 3.0, and 9.0 mg QD oral dose levels of plecanatide over 14 days of treatment (versus placebo) in a total of 78 CIC patients, there is no clear trend in AE over plecanatide dose ranges but the 9.0 mg dose appears to be associated with a higher rate of drug-related AEs (33.3%) compared to placebo (10%) or other dose levels (6.4-14.3%). As such, the 9 mg dose was not included in the Phase 2b study.
In Phase 2b dose-ranging study (SP304-20210) with 0.3, 1.0, and 3.0 mg QD oral doses of plecanatide over 12 weeks of treatment in a total of 951 CIC patients (including those on placebo), there appears to be dose-related increase in diarrhea, abdominal pain, number patients

with at least one Treatment-Emergent Adverse Events (TEAE), number of TEAEs and overall drug-related AE.
In the 2 phase III studies, there does not appear to be a clear dose-response for the majority of adverse events between 3 mg and 6 mg doses. However, there were some increase in diarrhea and nasopharyngitis with the higher dose of 6 mg compared to 3 mg.

Dose Selection:
The phase 2b study evaluated 0.3, 1.0, and 3.0 mg doses of plecanatide and had shown that the 3.0 mg dose provided a statistically significant treatment difference compared to placebo ($p = 0.009$) while 1 mg dose did not result in a statistically significant efficacy compared to placebo ($p = 0.057$). Based on the result of this phase 2b study, the 3 mg dose was selected for phase 3 studies. In addition, a 6 mg dose level was added in phase 3 studies to evaluate whether the efficacy could be improved further while maintaining the safety profile within an acceptable range.
In the phase 3 studies, both 3 mg and 6 mg doses resulted in statistically significant improvements over placebo. However, 6 mg dose was not numerically superior to the 3 mg dose on most endpoints although the studies were not sized for a direct comparison of 3 and 6 mg doses levels of plecanatide.
(b) (4) the sponsor had proposed (b) (4) 3 mg (b) (4) dose levels for CIC indication without specifying the distinct subpopulation (b) (4) (b) (4) (b) (4) The (b) (4) proposed dose of 3 mg is consistent with known dose-response relationship for both efficacy and safety.

Pharmacokinetics:
The sponsor attempted to measure the plasma concentration of plecanatide and its active metabolite SP-338 in healthy subjects and in CIC patient population. However, systemic exposures of the parent drug plecanatide or its active metabolite SP-338 were not detectable in human plasma up to 9 mg plecanatide dose (3 time the clinical dose of 3 mg) with LC-MS/MS bioanalytical method (with LLOQ of 1.0 ng/mL for plecanatide and 0.775 ng/mL for SP-338) suggesting insignificant absorption of plecanatide peptide and its metabolite SP-338 following oral route of administration.

Food Effect:
When 9 mg plecanatide tablet was administered with or without food in 24 healthy subjects, only 1 subject had detectable level of plecanatide at 0.5 and 1 hour post-dose under fasted state. Plecanatide concentrations were below the limit of quantitation for all other time points and for all other subjects. The active metabolite was not detected in any subjects. Food had minimal effect on bowel movement frequency, time to first bowel movement, fecal urgency, and fecal incontinence. Administration of 9 mg plecanatide with food had noticeable PD effect in Bristol Stool Form Scale (BSFS) scores and the incidence of abdominal cramping where food (both HF-HC and LF-LC) appear to increase BSFS score resulting in looser stool and increase the incidence of moderate and severe abdominal cramping and degree of abdominal cramping compared to fasted state. In both of the phase III studies, subjects were instructed to take the study drug with or without food at their own choice. In the proposed label, the sponsor is proposing to take plecanatide with or without food. However, based on the result of this food effect study, the agency recommends taking plecanatide with or without food in general but for

patients who experience abdominal cramping, plecanatide tablet should be taken under fasting condition. This is under further discussion with the medical review team.

Protein binding:
Plecanatide do not have detectable level of drug in the plasma at the proposed dose. Therefore, protein binding of plecanatide is not a concern. Nonetheless, plecanatide did not have significant binding to major human plasma proteins human serum albumin (HSA) and human α1-acid glycoprotein (AGP) proteins.

Metabolism:
In the simulated intestinal fluid (SIF), plecanatide is rapidly hydrolyzed at its C-terminus by cleavage of the Leu16 resulting in generation of a biologically active metabolite SP-338. SP-338 is further processed by an internal cleavage at Leu6-Cys7 resulting in a biologically inactive Leu6-clipped SP-338. However, potential metabolites of SP-338 were not quantitated. The potential metabolism by CYPs enzymes in human intestinal microsomes was not evaluated.

CYP inhibition /induction:
As the parent drug SP-304 and its metabolite SP-338 have limited systemic exposure, only CYP enzymes that are expressed in gastrointestinal tract, CYP2C9 and CYP3A, were evaluated for potential inhibition and induction by the parent drug SP-304 and its metabolite SP-338. Based on the in-vitro studies, plecanatide and its major metabolite SP-338 are not likely to inhibit CYP2C9 and CYP3A4 or induce CYP3A4 at the proposed dose.

Transporters:
As the parent drug SP-304 and its metabolite SP-338 have limited systemic exposure, only transporters that are expressed in the gastrointestinal tract, P-gp and BCRP, were evaluated for potential interaction with the parent drug SP-304 and its metabolite SP-338. Based on the in-vitro study on Caco-2 cells, both parent drug plecanatide SP-304 and its active metabolite SP-338 are not substrates or inhibitors of gut transporters P-gp and BCRP.

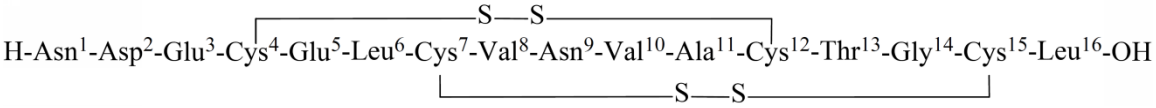
2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology review?

Plecanatide (SP-304) is a synthetic, 16-amino acid peptide with 2 disulfide bonds. The molecular formula is $C_{65}H_{104}N_{18}O_{26}S_4$ and the molecular weight is 1682 g/mol.

Figure 1: Structure of Plecanatide (SP-304)



DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.