

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208745Orig1s000**

**SUMMARY REVIEW**

## Division Director Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Donna Griebel, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA#</b>	208745
<b>Applicant</b>	Synergy Pharmaceuticals, Inc.
<b>Date of Submission</b>	1/29/2016
<b>PDUFA Goal Date</b>	1/29/2017
<b>Proprietary Name / Non-Proprietary Name</b>	Trulance/plecanatide
<b>Dosage Form(s) / Strength(s)</b>	Tablet; 3 mg
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of chronic idiopathic constipation
<b>Recommended Action:</b>	<i>Approval</i>
<b>Approved/Recommended Indication/Population(s) (if applicable)</b>	Treatment of chronic idiopathic constipation

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Lesley Hanes, MD/Laurie Muldowney, MD
Statistical Review	Shahla Farr, MS/ Yeh-Fong Chen, PhD
Pharmacology Toxicology Review	Yuk-Chow Ng, PhD/David Joseph, PhD
DB-VI Carcinogenicity Study Review	Hepei Chen/Karl Lin, PhD
OPQ Review	See table below
COA	Sarrit Kovacs, PhD/Elektra Papadopoulos, MD, MPH
Clinical Pharmacology Review	Dilara Jappar, PhD/ Sue Chih Lee, PhD/ Hae Young Ahn, PhD
DPMH	Christos Mastroyannis, MD/Tamar Johnson, MD/Carolyn Yancey, MD/Mona Khurana, MD/Lynne Yao, MD
OPDP	Adewale Adeleye, PharmD, MBA
CDTL Review	Joette Meyer, PharmD
OMPT/DMPP	Karen Dowdy/Marcia Britt Williams
OSE/DMEPA	Matt Barlow, PharmD/ Sherly Abraham, RPh/Mishale Mistry, PharmD, MPH
OSE/DRISK	Jacqueline Sheppard, PharmD/Robert Pratt, PharmD/Jamie Wilkins Parker, PharmD
OSI	Susan Leibenhaut, MD/Susan Thompson, MD/Kassa Ayalew, MD, MPH

OND=Office of New Drugs  
OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 COA= Clinical Outcome Assessment Team  
 OMPT=Office of Medical Policy Initiatives  
 OSE= Office of Surveillance and Epidemiology  
 OSI=Office of Scientific Investigations  
 DB-VI=Division of Biometrics - VI  
 DMPP=Division of Medical Policy Programs  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DPMH=Division of Pediatric and Maternal Health  
 DRISK=Division of Risk Management

### Quality Review Team

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Martin Haber	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product	Zhengfang Ge	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Bo Jiang	CDER/OPQ/OPF/ DPAI/PABI
Microbiology	Bo Jiang	CDER/OPQ/OPF/ DPAI/PABI
Facility	Juandria Williams	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Kalpana Paudel	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Truong Quach	CDER/OPQ/OPRO/DRBPMI/ RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Analysis (EA)	Raanan Bloom	CDER/OPQ/ONDP
Immunogenicity	Haoheng Yan, MD, PhD/Fred Mills PhD	OPQ/OBP/DPRR IV

## **1. Benefit-Risk Assessment**

I concur with the CDTL's risk benefit assessment. The following Risk-Benefit Summary and Assessment table was presented in the CDTL review. I have reproduced it within my review, with some limited modifications, as I concur. My modifications are marked with double underlining. I have deleted a few sentences, which are not tracked.

### **Benefit-Risk Summary and Assessment**

The currently available treatment armamentarium does not completely meet the needs of patients with chronic idiopathic constipation (CIC). The available treatments are not effective in all patients and may have limited by tolerability; therefore, additional treatment options are needed.

Plecanatide is a synthetic hexadecapeptide designed to mimic the action of uroguanylin, an endogenous peptide agonist for the guanylate cyclase C (GC-C) receptor, which is secreted in the GI tract and up-regulates intracellular production of cGMP (cyclic guanosine 3', 5'-monophosphate) in the intestinal epithelium. Elevated cGMP activates the cystic fibrosis transmembrane conductance regulator (CFTR), which leads to trans-epithelial efflux of chloride and bicarbonate from enterocytes lining the GI tract into the lumen of the gut, and secretion of water into the intestinal lumen. Increased secretion of water into the GI tract can loosen stools, stimulate bowel movements, and thus relieve constipation.

Plecanatide is the second in the GC-C agonist class of drugs. The first GC-C agonist was Linzess (linaclotide) which was approved on August 30, 2012 for CIC.

The efficacy and safety of plecanatide as a treatment for adults with CIC has been adequately assessed. The data from two adequate and well-controlled trials have demonstrated the efficacy of plecanatide over placebo, as measured by the proportion of patients with an increase in the number of complete spontaneous bowel movements (CSBMs) in at least 9 weeks out of the 12 weeks in the trial and at least 3 of the last 4 weeks. Other measures of efficacy included an increase in the number of bowel movements per week and an improvement in stool consistency and straining compared to placebo. Although the treatment difference between plecanatide and placebo were modest (approximately 10%), this drug may offer an alternative option for patients with CIC.

Plecanatide was shown to be safe and well-tolerated in adult patients with CIC. The most common adverse reaction was diarrhea. Severe diarrhea was reported and may lead to discontinuation, but can be managed by patient monitoring, withholding the medication and rehydration. In the clinical trials, severe diarrhea did not lead to serious outcomes. Additionally, plecanatide may increase hepatic enzymes.

Due to structural similarity between plecanatide and the endogenous peptides uroguanylin and guanylin, there is a theoretical immunogenicity risk for deficiency if patients develop cross-reacting anti-plecanatide antibodies. No signals of deficiency-related adverse events (e.g., hypertension, edema, pulmonary edema, hypernatremia, weight gain) were seen in the clinical trials database for plecanatide.

Serious adverse reactions, related to diarrhea, increases in liver biochemical tests, and guanylin/uroguanylin deficiency should be monitored

using routine postmarketing surveillance.

Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration. There are no clinically relevant drug interactions.

Use in pregnant women is not expected to result in fetal exposure; however, there is no information on the effects of maternal plecanatide exposure in the breastfed infant; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for plecanatide and the potential risk to the nursing infant.

(b) (4)

Pediatric patients have not been studied clinically. The nonclinical findings of death in young juvenile mice (human age equivalent of less than 2 years of age) and risk of severe dehydration, preclude use of plecanatide in pediatric patients of all ages until more information is available. The sponsor will be required to conduct a postmarketing study in patients from birth to 6 years of age to assess the ontogeny of the GC-C receptor in the gastrointestinal tract to inform whether plecanatide can be safely dosed in pediatric patients 2 years to less than 6 years of age. There will be a partial waiver for clinical studies in pediatric patients less than 2 years of age because there is evidence indicating that plecanatide would be unsafe in this age group. The juvenile animal data demonstrating lethality, as well as literature regarding GC-C ontogeny, indicate plecanatide would not be safe in patients under 2 years of age. The applicant will be required to conduct postmarketing trials to assess the safety, pharmacokinetics and efficacy of plecanatide in pediatric patients 2 years to less than 18 years of age. These trials will begin in the oldest pediatric age group. Results will be assessed in order to assure safety before progressively lower age cohorts are studied. Until the results of the biopsy study, pharmacokinetic and clinical data in pediatric patients 6 years to less than 18 years of age are available, pharmacokinetic dose-ranging and confirmatory clinical studies in pediatric patients 2 years to less than 6 years of age are deferred. A lactation study is also required to assess the presence of plecanatide in breast milk to determine the safety of plecanatide for breast-fed infants whose mothers are receiving therapy. Finally, the applicant will be required to develop anti-drug antibody assays in order to determine the immunogenic potential of plecanatide.

A REMS is not necessary for plecanatide to ensure the benefits outweigh the risks. The safety profile of plecanatide is similar to linaclotide, the other approved GC-C agonist. Therefore, the safety and risk mitigation approach of plecanatide will follow that of linaclotide, i.e., the risks will be communicated via labeling. A Medication Guide is required to inform patients of the risk of serious outcomes if plecanatide is

administered to pediatric patients. A Boxed Warning in the Prescribing Information will convey that plecanatide is contraindicated in less than 6 years of age due to the risk of serious dehydration and to avoid use in pediatric patients 6 years to less than 18 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<p>CIC affects an average of 15% of North Americans and is manifested by infrequent stools, incomplete bowel movements, straining, bloating, and hard, lumpy stool for at least six months. Moderate to severe symptoms of abdominal pain and/or straining with defecation can be debilitating for patients and if left untreated impact negatively on a patient’s general well-being. <u>CIC has a higher prevalence in women, those with reduced caloric intake and the elderly.</u></p>	<p>CIC is a serious condition associated with morbidity and symptoms can be debilitating.</p>
<b>Current Treatment Options</b>	<p>Linzess (linaclotide) and Amitiza (lubiprostone) are indicated for use in adult patients with CIC. The efficacy of these therapies cannot be directly compared to plecanatide due to the fact that there are no randomized trials that compare these drugs in the same trial. Cross-study comparisons are less valid. The available randomized placebo-controlled trials also use varying definitions for the primary endpoint.</p> <p>Amitiza demonstrated efficacy in primary endpoint of the number of spontaneous bowel movements (SBMs) compared to placebo during the first of four weeks of treatment (a mean increased of about 2 SBMs). Symptom scores were significantly improved with lubiprostone compared to placebo for stool consistency, straining, and constipation severity. The safety profile of lubiprostone is notable for adverse reactions of nausea, diarrhea, headache, and acute symptoms of dyspnea (generally occurring with 30 to 60 minutes after the first dose).</p>	<p>The current treatment armamentarium does not completely meet the needs of the patients with CIC. The available approved drugs have a modest treatment benefit over placebo. <u>OTC and nondrug therapies are not specifically approved for CIC; OTC products are approved for occasional constipation.</u></p> <p>Therefore, additional treatment options are needed for patients with CIC.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Linzess demonstrated a treatment difference of 10% to 17% over placebo in two trials in the primary efficacy endpoint of complete spontaneous bowel movements (CSBMs) where patients met the response criteria in at least 9 out of 12 weeks of the study. Linzess is in the same pharmacologic class as plecanatide (G-CC agonist); therefore the safety profile is similar to plecanatide and is notable for the adverse reaction of diarrhea. In post-marketing experience, severe diarrhea associated with dizziness, syncope, hypotension and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or intravenous fluid administration have been reported. Other adverse reactions in clinical trials included abdominal pain. As with plecanatide, there is a risk of serious diarrhea due to dehydration in pediatric patients, especially those less than 6 years of age, based on mortality in young juvenile mice and a lack of clinical safety and efficacy data in pediatric patients.</p> <p>Zelnorm (tegaserod maleate) was marketed from 2004 to 2007 for patients less than 65 years of age with CIC, but was voluntarily withdrawn due to <sup>(b) (4)</sup> the risk of ischemic cardiovascular events. It continues to be available through expanded access to individual patients who have failed other therapies.</p> <p>There are a variety of over-the-counter (OTC) therapies, such as laxatives, and nondrug interventions available to prevent/treat constipation by increasing bowel motility, decreasing GI transit time, or facilitating the passage of stool without straining. OTC therapies are labeled for occasional, discreet episodes of constipation and not for chronic use.</p>	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<p>The efficacy of plecanatide for the management of symptoms of CIC was evaluated in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients with CIC, as defined by the modified Rome III criteria. Patients were randomized to plecanatide 6 mg, plecanatide 3 mg, or placebo once daily. Only the results for the 3 mg dose will be described here. In the Intention-to-Treat (ITT) population, a total of <u>905 patients (Study 1) and 870 patients (Study 2) were randomized between placebo and plecanatide 3 mg.</u></p> <p>The primary efficacy endpoint was the proportion of patients who were responders over the 12-week treatment period. The study population was patients with less than 3 complete spontaneous bowel movements (CSBMs) per week at baseline. A CSBM is a spontaneous bowel movement that is associated with a sense of complete evacuation. A responder was defined as a patient who had a least 3 (CSBMs) in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12 week treatment period and at least 3 of the last 4 weeks of the study.</p> <p>This endpoint was recommended to the sponsor by FDA during drug development and is felt to encompass both magnitude of effect and durability of response. In patients with CIC and less than 3 CSBMs per week at baseline, an increase to at least 3 CSBMs per week (and in at least 1 CSBM per week) is considered to be clinically meaningful, <u>given that the definition of constipation includes having less than 3 bowel movements per week.</u> Based upon assessments of CSBMs, patients were assessed for both weekly and overall response. <u>Responders</u> demonstrated a response in at least 75% of the weeks (i.e., at least 9 out of 12 weeks), including the last month of the study (i.e., at least 3 of the last 4 weeks).</p>	<p>The efficacy of plecanatide in increasing the number of bowel movements in adult patients with CIC was demonstrated throughout 12-weeks in two adequate and well-controlled trials. In addition, patients began to respond to treatment within the first week and maintained improvement for 12 weeks.</p> <p>Although the treatment difference between plecanatide and placebo is modest (approximately 10%), plecanatide may offer an alternative treatment option to patients with CIC.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>In one study the responder rates were 21% for plecanatide and 10% for placebo, for an 11% treatment difference. In the second study the responder rates were 21% for plecanatide and 13% for placebo, for an 8% treatment difference. In both studies the treatment difference was statistically significant.</p> <p>In addition, in both studies improvements in the frequency of CSBMs/week were seen as early as week 1, with improvement maintained through week 12. The difference between plecanatide and placebo in the mean change of CSBMs/week frequency from baseline to week 12 was approximately 1.1 CSBMs/week.</p> <p>In both studies, patients in the plecanatide groups had improvements in the number of spontaneous bowel movements (SBM) and in stool consistency compared to patients in the placebo groups.</p> <p>In both studies, patients in the plecanatide groups also had improvements in the amount of straining with bowel movements, as further defined by the amount of time pushing or physical effort to pass stool, in comparison to patients in the placebo groups.</p> <p>There were insufficient numbers of patients to make meaningful conclusions about the efficacy in subgroups of age (less than 65 years vs. 65 years and older).</p> <p><u>In female patients, plecanatide was generally significantly more effective than placebo,</u> both over the course of the entire treatment period and for each weekly assessment. For male patients, less consistent results were observed for both doses; the small population size for male patients likely impacted these results.</p>	

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	<p><u>Plecanatide was similarly effective in white and nonwhite patients.</u></p>	
<p><b>Risk</b></p>	<p>In both placebo-controlled trials, the overall incidence of adverse events and serious adverse events was similar between plecanatide and placebo. <u>A total of 1733</u> patients received 3 mg plecanatide or placebo in the safety population.</p> <p>The most common adverse reactions (defined as adverse events occurring at a higher rate in the plecanatide group compared to placebo) in the two trials was diarrhea: 5% in the plecanatide 3 mg group and 1% in the placebo group.</p> <p>The majority of cases of diarrhea occurred within 4 weeks of treatment initiation. Severe diarrhea was reported in 0.6% of patients treated with 3 mg plecanatide compared to 0.3% of placebo-treated patients. Severe diarrhea occurred within the first 3 days of treatment.</p> <p>Of note, the incidence of severe diarrhea was higher in the 6 mg plecanatide group in comparison to the 3 mg plecanatide group and placebo (1.3% versus 0.3% for 3 mg and placebo, respectively).</p> <p>Discontinuations due to adverse reactions occurred in 4% of plecanatide-treated patients and 2% of placebo-treated patients. The most common adverse reaction leading to discontinuation was diarrhea: 2% of plecanatide-treated patients and 0.5% of placebo-treated patients withdrew due to diarrhea.</p> <p>Increases in liver biochemical tests were seen in 5 patients treated with</p>	<p>Overall, plecanatide is well-tolerated with few serious adverse reactions in adult patients. The adverse event profile is similar to the other approved GC-C agonist, linaclotide.</p> <p>The most common adverse reaction in the plecanatide clinical trials was diarrhea. Severe diarrhea was reported and may lead to discontinuation, but can be managed by patient monitoring, withholding the medication and rehydration. In the clinical trials severe diarrhea did not lead to serious outcomes.</p> <p>Serious adverse reactions, related to diarrhea, increases in liver biochemical tests, and UPD should be monitored using routine postmarketing surveillance.</p> <p>Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration. There are no clinically relevant drug interactions.</p> <p>Due to the structure similarity between</p>

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	<p>plecanatide 3 mg: 2 patients with alanine aminotransferase (ALT) greater than 5 to 15 times the upper limit of normal and 3 patients with aspartate aminotransferase (AST) greater than 5 times the upper limit of normal. These laboratory abnormalities were not associated with clinical symptoms and did not meet the criteria for Hy's law.</p> <p>There are no clinically relevant drug interactions. Plecanatide is metabolized in the GI tract to an active metabolite by loss of the terminal leucine moiety, and there is negligible systemic absorption of either plecanatide or its active metabolite.</p> <p>Due to the structure similarity between plecanatide and endogenous peptides, there is a theoretical immunogenicity risk for deficiency of uroguanylin and guanylin if patients develop anti-plecanatide antibodies that cross react with the endogenous proteins. Potential adverse events associated with uroguanylin/guanylin deficiency include hypernatremia, pulmonary edema, peripheral edema, sudden weight gain, and hypertension. No safety signals were seen in the clinical trials database for plecanatide for these adverse reactions.</p> <p>There were no clinically meaningful differences in the safety profile with respect to age (less than 65 years vs. 65 years and older), race or sex.</p> <p>Plecanatide has not been studied in pediatric patients less than 18 years of age. In young juvenile mice (1- to 2-week-old mice corresponding to human age equivalent of <u>approximately</u> 1 month to less than 2 years), plecanatide increased fluid-secretion into the intestines 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</p>	<p>plecanatide and endogenous peptides, there is a theoretical immunogenicity risk for uroguanylin/guanylin deficiency if patients develop cross reacting anti-plecanatide antibodies. No safety signals of uroguanylin/guanylin deficiency were seen in the clinical trials database for plecanatide.</p> <p>Deaths were observed in young juvenile mice (human age equivalent of less than 2 years. There were no deaths in older juvenile mice. These data, and other published findings, suggest an age-dependency of the pharmacodynamic response and indicate that plecanatide would not be safe to administer to children under the age of 2 years; however, more data are needed to determine whether plecanatide can be administered safely to children 2 years to less than 6 years. Plecanatide has not been studied in any pediatric patients less than 18 years of age. Therefore, plecanatide will be contraindicated in patients less than 6 years of age and should be avoided in patients 6 years to less than 18 years of age until more information is known.</p> <p>Use of plecanatide in pregnant women is</p>

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	<p>patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.</p> <p>The available data on plecanatide use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage.</p> <p>In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of plecanatide in mice and rabbits during organogenesis at doses much higher than the recommended human dosage.</p> <p>There is no information regarding the presence of plecanatide in human breast milk, or its effects on milk production or the breastfed infant. No lactation studies in animals have been conducted.</p> <p>There are no unresolved issues with product quality. Overall, the chemistry, manufacturing and controls information provided were found satisfactory.</p>	<p>not expected to result in fetal exposure. However, it is unknown whether the negligible systemic absorption of plecanatide in adults will result in a clinically relevant exposure to breastfed infants. Exposure to plecanatide in breastfed infants has the potential for <u>serious adverse reactions.</u> Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for plecanatide, <u>and the potential risk to the infant.</u></p>
<p><b>Risk Management</b></p>	<p>Pediatric patients have not been studied in the plecanatide developmental program. <u>There were</u> deaths in young juvenile mice (human age equivalent of approximately 1 month to less than 2 years) in nonclinical studies, which occurred within 24 hours following oral administration of plecanatide and are thought to be due to the increased expression of intestinal GC-C in this age group. These data along with data from a review of the literature regarding GC-C ontogeny suggest an age-dependency of the pharmacodynamic response and indicate that plecanatide would not be safe to administer to children under the age of 2 years; however, more data are needed to determine whether plecanatide can be administered safely to children 2 years to less than 6 years. As a result, plecanatide will have a Boxed Warning that there is a risk of serious dehydration in pediatric patients, and a Contraindication in</p>	<p>A REMS is not necessary for plecanatide to ensure the benefits outweigh the risks. The safety profile is similar to linaclotide, the other approved GC-C agonist. Therefore, the safety and risk mitigation approach is similar to linaclotide; the risks will be communicated via labeling including the use of a Medication Guide and Boxed Warning in the Prescribing Information.</p> <p>The Indications and Usage section of the Prescribing Information states that plecanatide is indicated in adults. There is a</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>patients less than 6 years of age. A study characterizing GC-C mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients will be required as a postmarketing study to assess the ontogeny of the GC-C receptor in order to determine if pediatric studies may be safe in children 2 years to less than 6 years age.</p> <p>Under the Pediatric Research Equity Act (PREA), clinical trials of the safety, pharmacokinetics and efficacy of plecanatide will be required to be conducted. There is an unmet need for treatment of pediatric patients with CIC. The sponsor has been granted a waiver from studying pediatric patients less than 2 years of age, as plecanatide may be unsafe in this age group. Clinical trials will be required in pediatric patients 2 years to less than 18 years of age. These trials will be conducted in sequential order in pediatric patients from oldest to youngest: 12 years to less than 18 years; 6 years to less than 12 years, and 2 years to less than 6 years. Until the results of the GC-C biopsy study are reviewed, pharmacokinetic and clinical data in pediatric patients 6 years to less than 18 years of age are available, the pharmacokinetic dose-ranging trials and confirmatory clinical trial in pediatrics 2 years to less than 6 years of age will not be conducted.</p> <p>There is no information regarding the presence of plecanatide in human breast milk, or its effects on milk production or the breastfed infant. The likelihood of plecanatide or its metabolite being measureable in breast milk is low due to the fact that there is negligible systemic absorption. However, given the anticipated use of plecanatide in females of reproductive potential, the lack of data on safe use in lactating women, and animal data demonstrating serious findings (mortality) in juvenile mice, a milk-only lactation study is required postmarketing to assess concentrations of plecanatide and its active metabolite in breast-milk in</p>	<p>Boxed Warning, Contraindication, and Warning and Precaution stating that plecanatide is contraindicated in patients less than 6 years of age due to the risk of serious dehydration and to avoid use in pediatric patients 6 years to less than 18 years of age.</p> <p>A Medication Guide is needed to inform patients of the risk of serious outcomes if plecanatide is administered to pediatric patients.</p> <p>The sponsor will be required to conduct a postmarketing study in patients from birth to 6 years of age to assess the ontogeny of the GC-C receptor in the gastrointestinal tract to inform whether plecanatide can be safely dosed in pediatric patients 2 years to less than 6 years of age [<u>a study to assess a signal of a serious risk of a significant fluid shift into the intestine due to age-dependent expression of the target receptor (GC-C), leading to severe dehydration and possibly death</u>].</p> <p>Clinical trials in pediatric patients to obtain information of the safety, pharmacokinetics and efficacy of plecanatide will be required to be conducted sequentially, such that</p>

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	<p>order to inform labeling [<u>to identify an unexpected serious risk associated with the presence of plecanatide or its active metabolite in human breast milk</u>].</p> <p>Due to the structure similarity between plecanatide and endogenous peptides, there is a theoretical immunogenicity risk for uroguanylin/guanylin deficiency if patients develop anti-plecanatide antibodies which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody screening assay during clinical development but it was not adequate. Since the immunogenicity risk is theoretical, the lack of adequate immunogenicity assays and clinical immunogenicity data does not preclude approval. The development of immunogenicity assays and sample testing will be required to be conducted post-marketing. <u>Hypersensitivity reactions are reported in the product label for another drug in the class, linaclotide; although no clear signal of clinical hypersensitivity reactions, such as manifestations consistent with anaphylaxis, were found in the review of the plecanatide safety database, the development of immunogenicity assays and sample testing will be required to identify an unexpected serious risk of immune mediated reactions with use of plecanatide.</u></p>	<p>younger age groups will not be initiated until safety has been demonstrated in older age groups and results from the GC-C biopsy study have been reviewed. The sponsor is not required to conduct studies in pediatric patients less than 2 years, as the drug may be unsafe.</p> <p>A milk-only lactation study will be required to assess the presence of plecanatide and metabolite in breast-milk.</p> <p>The sponsor will also be required to develop immunogenicity assays to assess for the development of anti-plecanatide drug antibodies, assays to evaluate the cross-reactivity of the potential anti-drug antibodies to endogenous guanylin/uroguanylin, and an assay to evaluate the neutralizing capacity of the potential anti-drug antibodies.</p>

## 2. Background

The applicant proposed marketing of plecanatide, a guanylate cyclase-C receptor agonist, for treatment of chronic idiopathic constipation (CIC). CIC is a condition defined by the Rome III criteria based on stool frequency, stool consistency, presence of straining, sensation of incomplete evacuation or anorectal obstruction/blockage. The symptoms must have been present for at least 3 months over a 6 month period, and the patient must not meet criteria for irritable bowel syndrome.

Plecanatide is a guanylate cyclase-C (GC-C) receptor agonist. It is structurally related to human uroguanylin peptide. Activation of GC-C results in increased cGMP concentrations, and increased intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator ion channel (CFTR), resulting in increased intestinal fluid and accelerated transit.

There are currently two products marketed with the specific indication of CIC, i.e., linaclotide (also a guanylate cyclase-C receptor agonist) and lubiprostone (chloride channel activator). Zelnorm, a 5-hydroxytryptamine receptor partial agonist) was voluntarily withdrawn from the market due to safety concerns related to ischemic events, including (b) (4) ischemic cardiovascular events.

The regulatory history of the plecanatide development program is well documented in the Clinical Review (Dr. Lesley Hanes, MD). In a letter dated 6/18/2014, FDA concurred with the IND sponsor's request for a waiver of the requirement to conduct a thorough QT study, given the limited systemic exposure of plecanatide and its active metabolite in humans.

Two phase 3 trials were submitted to support the efficacy and safety of the plecanatide for the proposed indication. During this NDA review, the OSI reviewer found that two sites (one that enrolled 16 subjects and another that enrolled 14 subjects) that participated in one of the phase 3 trials, Study SP304203-03, had been classified Official Action Indicated (OAI) in a previous inspection. The data from these sites were deemed unreliable and were removed from the major safety and efficacy analyses presented in product labeling. Furthermore, multiple subjects who participated in the phase 3 trials were found to have enrolled in other plecanatide studies or at more than one site within the two phase 3 trials. Data from duplicated subjects also had to be removed from the final analyses that supported the decisional process (and product labeling). Given these issues, the reviewers were particularly interested in the conclusions of the OSI inspections conducted during this NDA. Six other sites (beyond those that had previously been classified OAI) across the trials, the CRO and the applicant were inspected during the review cycle; OSI recommended that the data from all of those sites (i.e., excluding the two with previous OAI designation) could be used in the application.

### 3. Product Quality

The Office of Product Quality (OPQ) reviewers have determined that the applicant has provided sufficient information to assure the identity, strength, purity and quality of the drug product. A Categorical Exclusion for the Environmental assessment was granted. The OPQ reviewers' recommendations were incorporated in the final product labeling. The Office of Process and Facilities made a final overall "Approval" recommendation for the facilities involved in this application. OPQ has recommended approval from a product quality standpoint, and I concur with their recommendation.

Plecanatide is a cyclized 16 amino acid peptide (b) (4)

To reduce a potential carcinogenic impurity (b) (4) was changed for the commercial batches (b) (4)

(b) (4) A comparability study demonstrated equivalency of the drug substance and drug product (b) (4). Based on ICH M7, the drug substance specification proposed by the applicant for (b) (4) was (b) (4). A 6 mg plecanatide dose would result in an exposure of (b) (4)/day, based on the proposed specification, which is less than the ICH M7 limit of 1.5 microgram/day.

Impurities included (b) (4) The applicant proposed a release and shelf-life acceptance criterion of (b) (4)%. This release criterion required qualification of this impurity because the release limit (b) (4)%. The Pharmacology/Toxicology reviewer confirmed that the (b) (4) had been qualified in the GLP chronic toxicology studies because the (b) (4) was present at substantial levels in the drug substance lots used in those studies.

During the course of the NDA review, the applicant amended the application with in-use stability data for the tablets prepared in two brands of apple sauce and in water. The data indicated that the tablets are stable after being crushed and placed in apple sauce and water for 30 minutes. Furthermore, data were submitted regarding drug recovery after administration via gastric feeding tube. On average 98.9% of plecanatide was recovered after being dissolved in water and pushed through a gastric feeding tube. These data supported including instructions for administration with water via a nasogastric or gastric feeding tube in the Dosage and Administration section of the product label, as well as information on administration in applesauce.

### 4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewers have recommended approval. I concur. The drug contains no novel excipients; the excipients appear safe. The impurities were qualified at the

proposed limits in the drug product. Plecanatide was not found to be genotoxic. Carcinogenicity was assessed in 2-year studies in mice and rats. Plecanatide was not tumorigenic in mice at oral doses up to 90 mg/kg/day or in rats at oral doses up to 100 mg/kg/day. (Executive CAC met on July 26, 2016: the cutaneous fibrosarcomas observed in the mouse study were not considered evidence of carcinogenicity because there was no dose response for this finding; pancreatic islet cell tumors in rats were not considered evidence of carcinogenicity because significance was not achieved on the pairwise test.)

Given that limited systemic exposure was achieved at the tested dose levels in animals, whereas no detectable exposure occurred in humans, the product label will state that animal and human doses should not be compared directly for evaluating relative exposure. There was no observed effect on fertility or reproductive function in mice.

**Juvenile animal data and human pediatric safety concerns.** The Pharmacology/Toxicology reviewers worked with the review staff from the Division of Pediatric and Maternal Health staff, as well as the DGIEP Clinical reviewers, to develop appropriate labeling and PREA PMRs. Similar to the nonclinical development program of another drug in the class, linaclotide, neonatal/juvenile mice were much more sensitive to plecanatide toxicity than adult animals. Plecanatide was well tolerated in adult mice, rats and monkeys at oral doses to 3000-, 2000- and 2000-times higher, respectively, than the dose that will be approved for human use (3 mg); however, age dependent lethality was noted with plecanatide. Deaths occurred within 24-48 hours of initiation of dosing in very young animals and appeared to be related to dehydration. The minimum lethal plecanatide dose in postnatal day 7 mice was 0.5 mg/kg/day, whereas in postnatal day 14 mice the minimum lethal dose was 10 mg/kg/day. These ages in mice correspond to human age of approximately 1 month to less than 2 years (Barrow PC in: Nonclinical Drug Safety Assessment: Practical Considerations for Successful Registration. pg. 413, Editors: Sietsema WK and Schwen RS, FDANews 2007). No deaths were observed in juvenile mice when dosing was started on Day 21, up to a dose of 300 mg/kg/day, which was the highest dose studied. The postnatal Day 7 and Day 14 mice manifested signs of dehydration and decreased motor activity. No gross lesions were identified on necropsy, although there was increased weight of intestinal contents, consistent with the mechanism of action of the drug. Linaclotide is contraindicated in children up to 6 years of age, as it caused deaths in neonatal mice after oral administration of 1 or 2 daily doses, starting on postpartum day 7. Deaths were also observed in juvenile mice after a single oral administration on postpartum day 14 and postpartum day 21. Linaclotide did not cause death in a study in older juvenile mice 6 weeks of age.

Receptor expression for GC-C in the intestinal tract of human children is age dependent; expression decreases with increasing age. Based on the nonclinical data, which is consistent with linaclotide, plecanatide will be approved with a Boxed warning and a Warning and Precaution regarding serious risk of use in pediatric patients, in addition to a Contraindication for use in patients <6 years of age. The pediatric study plan also is similar to linaclotide's (see Section 10 Pediatrics of this review). The label's Boxed Warning will state:

## **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 [see Contraindications (4), Use in Specific Populations (8.4)].**
- **Avoid use of TRULANCE in patients 6 years to less than 18 years of age [see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].**
- **The safety and effectiveness of TRULANCE have not been established in patients less than 18 years of age [see Use in Specific Populations (8.4)].**

Section 4 Contraindication will state:

TRULANCE is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].

Section 5.1 Warnings and Precautions will state:

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 into the intestines 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 patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.

Avoid the use of TRULANCE in patients 6 years to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in younger mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of TRULANCE in patients 6 years to less than 18 years of age [see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)].

(Warnings and Precautions 5.2 describes the adverse reaction diarrhea.)

Section 8.4 Pediatric Use of the label will include juvenile animal toxicity data to provide context for the boxed warning and the contraindication, as follows:

Single oral doses of plecanatide at 0.5 mg/kg and 10 mg/kg caused mortality in young juvenile mice on postnatal days 7 and 14, respectively (human age equivalent of approximately 1 month to less than 2 years). Treatment-related increases in the weight of intestinal contents were observed in juvenile mice following single doses of

plecanatide on postnatal day 14 (human age equivalent of approximately less than 2 years), consistent with increased fluid in the intestinal lumen. Although the recommended human dose is approximately 0.05 mg/kg/day, based on a 60-kg body weight, plecanatide and its active metabolite are not measurable in adult human plasma, whereas systemic absorption was demonstrated in the juvenile animal toxicity studies. Animal and human doses should not be compared directly for evaluating relative exposure.

**Labeling issues related to pH effect on plecanatide efficacy.** The Nonclinical Pharm/Tox review states (in the Integrated Summary), “In vitro studies demonstrated that receptor binding affinities and cGMP-stimulatory activities of plecanatide were enhanced at pH 5, as compared to pH 8.” The applicant proposed to include in Section 12.1 Mechanism of Action of the product label a statement (b) (4)

(b) (4) The Clinical and Statistical reviewers evaluated a post hoc analysis that explored the impact of concomitant PPI use in the phase 3 trials on efficacy and found no clear evidence that concomitant use of PPIs decreased plecanatide’s efficacy. The reviewers recommended removal of language (b) (4)

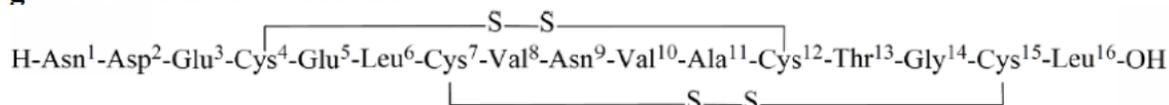
(b) (4). The applicant agreed to remove the statement as long as the label stated that plecanatide is structurally related to human uroguanylin and, similar to uroguanylin, functions as a guanylate cyclase-C (GC-C) agonist. Section 12.1 was modified accordingly during labeling negotiations.

## 5. Clinical Pharmacology

The Clinical Pharmacology reviewers “found the submission acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling language is reached...” The Clinical Pharmacology reviewers’ recommendations for labeling were addressed in the final label. There are no outstanding Clinical Review issues that preclude approval.

Plecanatide (or its active metabolite SP-338, which is the product of hydrolytic cleavage of the Leu16 at the C-terminus of plecanatide) systemic exposure was not detectable in humans. The LLOQ of the LC-MS/MS assay is 1.0 ng/ml for plecanatide and 0.775 ng/mL for SP-338. See structure below.

**Figure 1: Plecanatide structure**



Although the Clinical Pharmacology review states that the drug and its metabolite were not detected in either healthy subjects or patients with CIC, up to a dose of 9 mg (3X the dose level that will be approved), including after multiple dosing for 4 weeks in CIC patients, the

reviewers do note that a single healthy subject who participated in the food effect study achieved a detectable plecanatide level in the fasted state after a 9 mg dose of plecanatide tablet. The highest exposure documented in that subject occurred at 1 hour post dose and was 2.18 ng/mL. This exposure, which was documented at a dose 3X the dose that will be approved, is lower than that observed in nonclinical toxicology studies in which animals were administered much higher doses.

In the mouse juvenile animal studies, the juvenile mice that started dosing with 10 mg/kg on Day 14, revealed a Cmax in males of 110.0 +/-71.8 ng/ml and, in females, a Cmax of 40.0+/-28.5 ng/ml. Adult male monkeys administered a dose of 25 mg/kg had a Cmax of 6 ng/ml, and at a dose of 250 mg/kg the Cmax ranged 33 ng/mL to 945 ng/ml. Female monkeys had a similar Cmax at 25 mg/kg, and the Cmax at 250 mg/kg ranged 73 ng/ml to 190 ng/ml. In a 28 day oral dosing study in monkeys administered 1, 10 and 75 mg/kg/day, the Cmax on Day 28 associated with the 75 mg/kg/day doses level was 42.4 ng/ml ±22.4 in males and 86.2 ng/ml ±27.6 in females. The Pharm/Tox reviewer noted that these exposure levels were well tolerated in adult animals. Although there were studies that revealed mononuclear cell infiltrates in various organs and glands, in addition to acinar cell atrophy, the findings were not replicated in additional studies. There were no drug-related deaths in monkeys at single doses of up to 2000mg/kg or repeated daily oral doses of plecanatide up to 100 mg/kg/day for 39 weeks (approximately 1,000 times the MRHD). Diarrhea observed at 25, 250 and 2000 mg/kg was considered to be due to the pharmacological activity of the drug; the tolerated dose in cynomolgus monkeys was considered to be 250 mg/kg. No adverse effects were observed in mice at doses up to 150 mg/kg/day for 26 weeks (approximately 3,000 times the MRHD) and in monkeys up to 100 mg/kg/day for 39 weeks (approximately 1,000 times the MHRD). Therefore, given the nonclinical safety associated with higher exposures, the exposure documented in a single subject in the clinical database who was treated with a dose higher than the dose that will be approved does not raise a safety concern, should there be a rare subset of the population who experience a similar exposure to this outlier subject.

Studies of CYP and transporter interactions were limited to those expressed in the gastrointestinal tract, due to the limited systemic exposure of the parent drug and its metabolite. In vitro studies indicated that plecanatide and SP-338 do not inhibit CYP 2C9 or 3A4, and do not induce CYP3A4. Based on in vitro study in Caco-2 cells, the parent drug and active metabolite were not substrates or inhibitors of the gut transporters P-gP and BCRP.

Hepatic impairment and renal impairment studies were not conducted due to the lack of appreciable systemic exposure associated with plecanatide and its active metabolite.

The to-be-marketed formulation is the same as the phase 3 clinical trial formulation.

## **6. Clinical Microbiology**

Not applicable.

## 7. Clinical/Statistical-Efficacy

The Statistical and Clinical reviewers all concluded that the efficacy data submitted in the NDA establish the efficacy of plecanatide for the treatment of chronic idiopathic constipation (CIC). I concur.

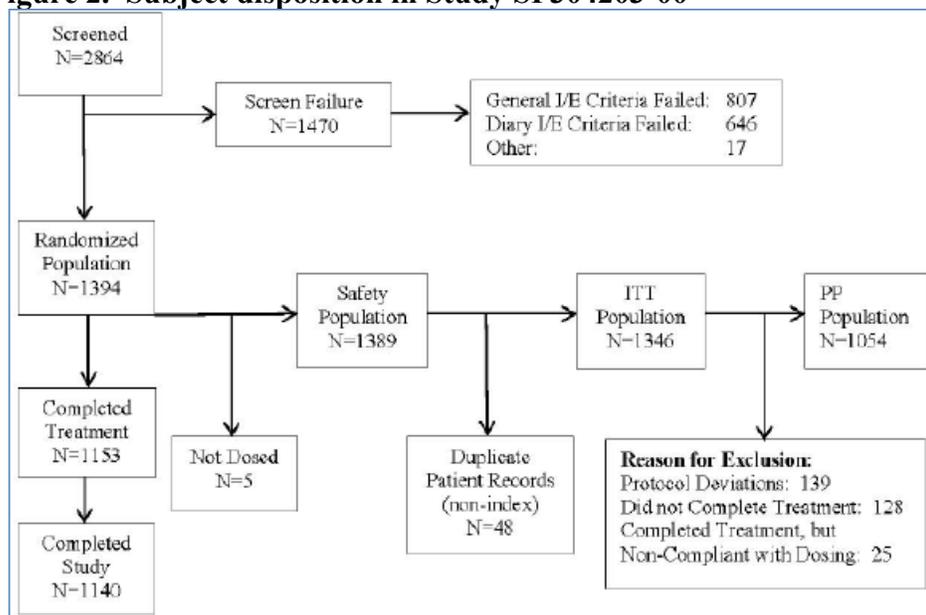
The applicant submitted the results of two identically designed phase 3 double blind, placebo controlled trials to establish the efficacy of plecanatide for treatment of CIC. The trials (Study SPD304203-00 and Study SPD304203-03) compared two plecanatide dose levels, 3 mg and 6 mg, to placebo. The primary endpoint was proportion of “durable overall complete spontaneous bowel movement (CSBM) responders over a 12-week study period”. A CSBM responder was defined as a subject who was a weekly responder for at least 9/12 weeks of treatment. A durable overall CSBM responder met the criteria of CSBM responder AND was a weekly responder in at least 3 of the last 4 weeks of the 12 week study period.

The secondary endpoints included: 1) change from baseline in frequencies of CSBMs and SBMs, 2) change from baseline in stool consistency (measured using the Bristol Stool Form Scale, BSFS), 3) change from baseline in straining score, 4) treatment satisfaction, 5) time to first SBM, and 6) percentage of patients with CSBM or SBM within 24 hours of the first dose.

The statistical analysis plan utilized a Holm-based tree-gatekeeping procedure to control Type I error rate by taking into account the multiple doses tested in each trial, in addition to the multiple endpoints (primary and secondary). For responder analyses, subjects were designated a nonresponder in a week for which they completed <4 days of diary entries. Missing days (1-3) in subjects who completed at least 4 entries in a week were handled through calculations based on a mean replacement approach (MRA) where the CSBM/SBM rate for the week was calculated by taking the number of CSBMs/SBMs reported in the week, multiplying that number by 7, and dividing by the number of days for which the subject had entered data in their diary. Sensitivity analyses based on various missing diary data imputation methods were performed by the applicant, including one in which the MRA was not analyzed without the multiplication by 7 (analysis limited to observed data in the week).

As noted in Section 2 Background of my review, in Study SP304203-00, 66 subjects were identified who had enrolled in other plecanatide studies or at more than one study site in SP304203-00, during the plecanatide development program. These 66 subjects had 69 unique patient identifiers. Ultimately, 21/66 (referred to in the reviews as “index subjects”) were retained in the ITT population of SP304203-00 because it was the first of the trials they had enrolled in; the remaining were removed from the ITT population for purposes of primary analysis, which reduced the ITT population from 1394 randomized to 1346 (a 3.4% reduction in sample size). The following figure, reproduced from the Clinical Review, summarizes the disposition of subjects in Study SP304203-00. Note that there is an error in the figure, as the five “Not Dosed” patients were actually included in the ITT population total in this figure.

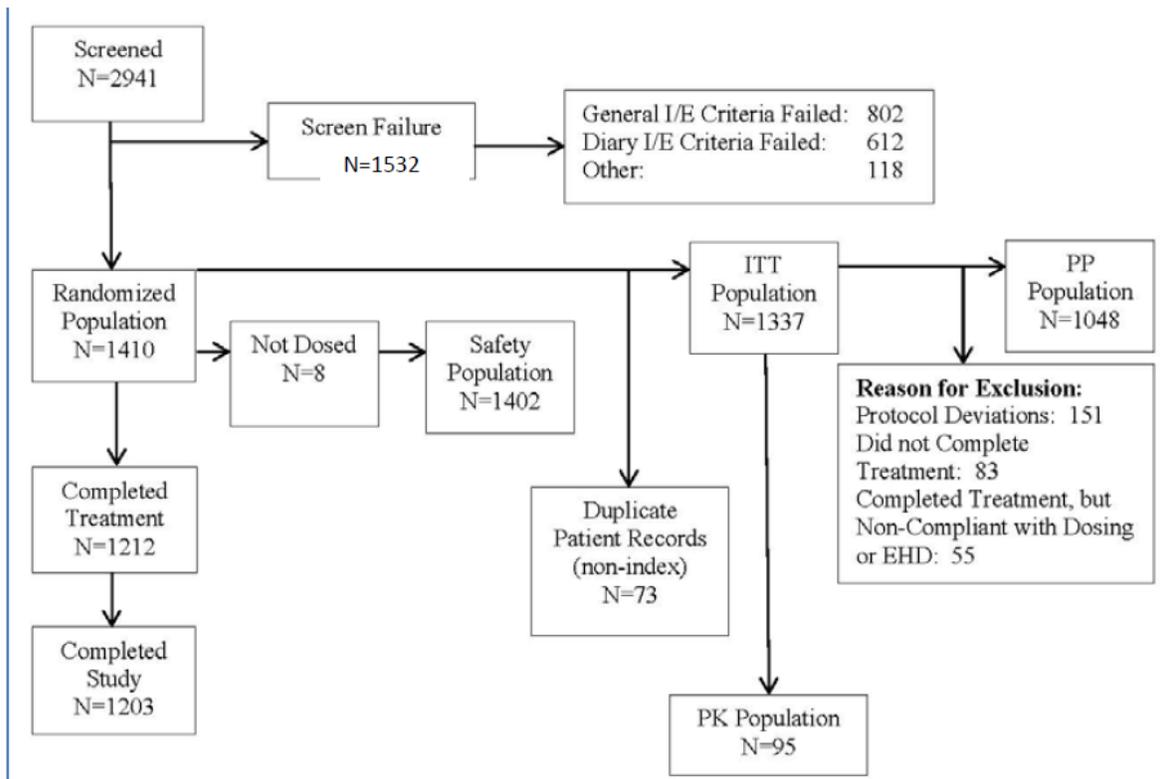
**Figure 2. Subject disposition in Study SP304203-00**



Source: Sponsor's CSRs, SP304203-00; AE = adverse event, EW = early withdrawal, FU = follow up, I/E = inclusion/exclusion, ITT = Intent-To-Treat, LOE = lack of efficacy, PP = Per Protocol

Study SPD304203-03, which only included US sites, also had issues with duplicate subjects, but the number of duplicates was higher than in SPD304203-00. There were 96 (39%) duplicate subjects (including subjects who enrolled in other plecanatide studies and/or at more than one site in Study SPD304203-03), of which 73 were not “index subjects”. Elimination of these 73 subjects from the ITT analysis who were not enrolled in SPD304203-03 as their first study (and elimination of within study duplication) reduced the ITT population to 1337. Note that this 1337 includes the subjects from two OAI sites (Sites #362 and #402) with data integrity issues, as discussed in Section 2 Background, above. The latter subjects were also removed for the ITT analyses during the course of the NDA review, leaving 1310. The following figure, reproduced from the Clinical Review, summarizes the disposition of subjects in Study SP304203-03 (not including the subjects removed from the two OAI sites).

**Figure 3. Subject disposition in Study SP304203-03**



Source: Sponsor's CSRs, SP304203-03; AE = adverse event, EW = early withdrawal, FU = follow up, I/E = inclusion/exclusion, ITT = Intent-To-Treat, LOE = lack of efficacy, PP = Per Protocol

The Clinical reviewer summarized the distribution of remaining non-duplicate and index case subjects by treatment arm and by trial in her review. I have reproduced the table below. The treatment arms were impacted similarly, although a numerically lower proportion in the placebo arm of SP3042 03-00 was impacted.

**Table 1: Summary of Non-duplicate, Index and Duplicate Subjects in Studies SP304203-00 and -03, by ITT population and Safety population.**

	SP304203-00			SP304203-03		
Analysis Populations n (%)	Placebo (N=467)	Plecanatide 3 mg (N=471)	Plecanatide 6 mg (N=456)	Placebo (N=469)	Plecanatide 3 mg (N=470)	Plecanatide 6 mg (N=471)
ITT Population <sup>1</sup>	452 (97%)	453 (96%)	441 (97%)	445 (95%)	443 (94%)	449 (95%)
Non-duplicate patients	448 (96%)	443 (94%)	434 (95%)	437 (93%)	434 (92%)	434 (92%)
Index case patients	4 (0.9%)	10 (2%)	7 (2%)	8 (2%)	9 (2%)	6 (1.3%)
Safety Population <sup>2</sup>	464 (99%)	471 (100%)	454 (99%)	467 (99%)	466 (99%)	469 (99%)
Non-duplicate patients	445 (95%)	443 (94%)	432 (95%)	436 (93%)	430 (92%)	441 (94%)
Duplicate patient	19 (4%)	28 (6%)	22 (5%)	31 (6.6%)	36 (8%)	28 (6%)
Index case patients	4 (0.9%)	10 (2%)	7 (2%)	8 (2%)	9 (2%)	6 (1%)
PP Population	354 (76%)	357 (76%)	343 (75%)	353 (75%)	340 (72%)	355 (75%)
PK Population	-	-	-	32 (7%)	31 (7%)	32 (7%)

Source: Reviewer's Table, Modified from Table 8 in Sponsor's CSR SP304203-00 and Table 9 in Sponsor's CSR SP304203-03

<sup>1</sup> The ITT population was defined as all patients who were enrolled and randomized and included 5 patients in study -00 who did not receive drug (n = 3 placebo and n = 2 6 mg) and 7 patients in study -03 who did not receive drug (n = 1 placebo, n = 4 3 mg, and n = 2 6 mg)

<sup>2</sup> The safety population includes all patients who received drug and thus includes duplicate patients. Patients in the ITT population who were randomized but did not receive drug were not included in the safety population

The following tables summarize the results of the primary efficacy analyses in the two trials. The treatment effect (delta between the plecanatide and placebo) was similar between trials, although the delta was numerically smaller in Study SP304203-03. The first table, for Study SP304203-00, reflects the results of the applicant's analyses, eliminating non-index subjects from the analysis population. The second table, for SP30403-03, reflects the results of the Statistical reviewer's analyses, also eliminating the subjects from the OAI sites from the analysis population. There was no evidence of a numerically higher response rate associated with the highest dose level tested (6 mg) relative to the lower (3 mg) dose.

**Table 2: Applicant’s Primary Endpoint Efficacy Analysis in Study SP304203-00 (with mean replacement approach applied) – ITT population**

	Placebo (N=452)	Plecanatide 3 mg (N=453)	Plecanatide 6 mg (N=441)	Active Combined (N=894)
Durable Overall CSBM Responders, n (%) <sup>a</sup>	46 (10.2)	95 (21.0)	86 (19.5)	181 (20.2)
95% CI (%) <sup>b</sup>	(7.5, 13.3)	(17.3, 25.0)	(15.9, 23.5)	(17.7, 23.0)
Non-Responders, n (%) <sup>c</sup>	406 (89.8)	358 (79.0)	355 (80.5)	713 (79.8)
CMH p-value <sup>d</sup>	-	< 0.001	< 0.001	-
Odds Ratio (adjusted) <sup>e</sup>	-	0.429	0.469	-
95% CI	-	(0.294, 0.627)	(0.319, 0.688)	-
Difference in Proportions (adjusted) <sup>f</sup>	-	0.107	0.094	-
95% CI	-	(0.061, 0.154)	(0.047, 0.140)	-
Breslow-Day p-value <sup>g</sup>	-	0.609	0.096	-

CI = confidence interval, CMH = Cochran Mantel Haenszel (test), CSBM = complete spontaneous bowel movement, ITT = Intent-To-Treat, MRA = mean replacement approach, N = number of patients.

- A durable overall CSBM responder was a patient who was a weekly CSBM responder for at least 9 of the 12 treatment weeks, including at least 3 of the last 4 weeks. A CSBM weekly responder was defined as a patient who had  $\geq 3$  CSBMs for a given week and an increase from Baseline of  $\geq 1$  CSBM for that same week, determined using MRA methodology as defined in Section 4.1.2 of the statistical analysis plan.
- Clopper-Pearson method.
- Patients missing with respect to the endpoint were scored as non-responders.
- CMH p-value for the comparison of treatment group to placebo, stratified by gender.
- Common odds ratio, treatment/placebo adjusted for stratification factor (gender) in the CMH analysis.
- Proportion of responders in treatment group minus proportion in Placebo group, adjusted for stratification factor (gender) in the CMH analysis.
- Breslow-Day p-value for the test of consistency of the treatment effect across the stratification.

Source: Sponsor's Table 14 of the Study Report

As stated above, the following Statistical reviewer’s summary table of the primary endpoint efficacy analysis for the second trial, Study SP304203-03, is based on the analysis dropping the subjects from the two sites the OSI reviewers recommended could not be relied upon due to data integrity issues (in addition to non-index duplicate subjects), and utilized the data generated by the MRA approach for missing data.

**Table 3. Study SP304203-03 Statistical reviewer’s Primary Endpoint Efficacy Analysis – applying the mean replacement approach (MRA) – ITT population**

Primary parameter (CSBM Responders)	Placebo (n=440)	3 mg (n=430)	6 mg (n=440)	P-Value* (overall)
Response Rate	57 (13.0%)	88 (20.5%)	88 (20%)	<0.005

\*Using Chisq. Test

The sensitivity analyses conducted by the Statistical reviewer for both phase 3 trials using observed data (not using the MRA method) revealed a slightly numerically higher response rate on each of the study arms and a slightly higher delta (observed treatment effect) between the 3 mg dose level and placebo.

The reviewers concluded that the protocol deviations identified in the review of Study SP304203-03 did not preclude including the results of this trial in the label. (b) (4)

(b) (4). I concur with that recommendation. The following table will be included in the product label. The efficacy data are from the analysis using the MRA approach to missing data. Study 1 refers to Study SP304203-00 and Study 2 refers to Study SP304203-03.

**Table 4. Efficacy Responder Rates in the Two Placebo Controlled Studies of CIC: at least 9 of 12 weeks and at least 3 of the last 4 weeks (ITT Population)**

Study 1			
	<b>TRULANCE 3 mg N = 453</b>	<b>Placebo N = 452</b>	<b>Treatment Difference# [95% CI*]</b>
Responder <sup>^</sup>	21%	10%	11% [6.1%, 15.4%]
Study 2			
	<b>TRULANCE 3 mg N = 430</b>	<b>Placebo N = 440</b>	<b>Treatment Difference# [95% CI*]</b>
Responder <sup>^</sup>	21%	13%	8% [2.6%, 12.4%]

\* CI = confidence interval

# p-value <0.005

<sup>^</sup> primary endpoint defined as a patient who had a least 3 CSBMs in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12 week treatment period and at least 3 of the last 4 weeks of the study

The Statistical reviewers evaluated the statistical analysis plan for the two trials, with regard to whether it was appropriate to include the secondary endpoint analyses in product labeling. The Clinical Outcomes Assessment review staffs were also consulted to provide feedback on whether the assessment tools used to measure these endpoints were adequate to support labeling. The reviewers ultimately concluded that the labeling for the secondary endpoints would be limited to frequency of CSBMs and SBMs per week, stool consistency and straining. The statements below regarding the secondary endpoints, which will appear in Section 14 of the product label, are consistent with linaclotide’s labeling.

“In both studies, improvements in the frequency of CSBMs/week were seen as early as week 1 with improvement maintained through week 12. The difference between the TRULANCE group and the placebo group in the mean change of CSBMs/week frequency from baseline to week 12 was approximately 1.1 CSBMs/week.

Over the 12 week treatment period, improvements were observed in stool frequency (number of CSBMs/week and SBMs/week) and/or stool consistency (as measured by the BSFS), and/or in the amount of straining with bowel movements (amount of time pushing or physical effort to pass stool) in the TRULANCE group as compared to placebo.”

The phase 3 trials included a phase in which daily diary data were collected after drug discontinuation. This allowed for evaluation of a rebound effect (increased severity of symptoms compared to baseline). The reviewers determined that this was information that health care providers would want to know, and the following general statement was included in Section 14 of the product label:

“Following completion of the study drug treatment period, patients continued to record data in the daily diary for a 2 week Post-Treatment Period. During this time, TRULANCE-treated patients generally returned to baseline for these study endpoints.”

Subgroup analyses by sex, age and race were evaluated. As stated earlier in this review, in the Risk/Benefit Framework:

“There were insufficient numbers of patients to make meaningful conclusions about the efficacy in subgroups of age (less than 65 years vs. 65 years and older).

In female patients, plecanatide was generally significantly more effective than placebo, both over the course of the entire treatment period and for each weekly assessment. For male patients, less consistent results were observed for both doses; the small population size for male patients likely impacted these results.

Plecanatide was similarly effective in white and nonwhite patients.”

## 8. Safety

After excluding records from duplicate patients (as discussed in Sections 2 and 7 above) and from the OAI sites that OSI recommended excluding due to data integrity issues, there were 863 patients treated with the 3 mg plecanatide dose level in the phase 3 trials, and 868 patients treated with plecanatide 6 mg. The Clinical reviewers determined that the safety analyses “show that plecanatide is safe and well tolerated...in the treatment of patients with CIC”. The CDTL review states, “Overall, the safety profile of plecanatide treatment appears to be acceptable.” I concur.

There were no deaths in the phase 3 trial safety database. The serious adverse event rate (SAE) was similar among arms: placebo 1.3%, plecanatide 3 mg 1.5%, plecanatide 6 mg 1.0%. The most common adverse reaction in the phase 3 placebo controlled trials was diarrhea. The 3 mg plecanatide group experienced a numerically lower rate of gastrointestinal related adverse reactions than the 6 mg group, and given that the efficacy observed with the two dose levels was similar, only the lower 3 mg dose will be approved. Five percent of patients treated with plecanatide 3 mg in the phase 3 trials experienced diarrhea, compared to 1% on the placebo arm. Severe diarrhea occurred in 0.6% of the plecanatide 3 mg arm subjects, compared to 0.3% with placebo. Diarrhea was the most common adverse reaction leading to discontinuation: 2% of plecanatide 3 mg arm patients vs. 0.5% of placebo arm patients. Abdominal pain was the second most common adverse reaction graded severe, and was reported in 0.3% of patients treated with plecanatide.

Notably, there were no SAEs of diarrhea, dehydration or ischemic colitis; however, there was a case of gastroenteritis that was classified as an infection SAE (plecanatide 6 mg arm). There were two SAEs categorized as gastrointestinal in plecanatide treated patients and none in the placebo arm. One (on the 3 mg arm) was intestinal obstruction and the other (6 mg arm) was acute pancreatitis. The acute pancreatitis, which occurred in a female with a history of gallstones, was diagnosed based on clinical presentation of abdominal pain and elevated lipase (133 U/L, with ULN = 51); however, amylase was not checked and CT and abdominal ultrasound were “unremarkable”. The SAE of intestinal obstruction occurred in a patient who was found to have adhesions from prior abdominal hernia repair. The obstruction resolved after lysis of adhesions.

Elevated transaminase levels (AST, ALT) were identified in subjects treated with plecanatide in the phase 3 trials. There were 2 subjects with ALT elevated 5-15 times the ULN, and 3 patients with AST elevated >5 times the ULN. The Clinical reviewer carefully evaluated the safety data base for any evidence of elevations that also met Hy’s Law. Two subjects of particular interest are summarized in her review; however, both had concomitant elevation of alkaline phosphatase and other clinical explanations for elevation of transaminase and bilirubin. One had cholelithiasis on ultrasound, fatty liver disease, and had taken a supratherapeutic dose of acetaminophen; the elevated biochemical tests normalized 14 days later and were not consider related by the investigator or sponsor. I agree with the Clinical reviewers that this case was not plecanatide related and did not meet criteria for Hy’s Law. The other patient also had a concomitant elevation of alkaline phosphatase. Laboratory values normalized despite continuation of plecanatide. I concur with the clinical reviewer that this was not related to plecanatide and did not meet a definition of Hy’s Law.

There were 18 subjects in the safety database with pregnancy (classified as an SAEs by protocol designation): 4 in the placebo arm, 5 in the 3 mg plecanatide arm and 9 in the 6 mg arm. Overall, there were 20 pregnancies reported during the clinical development program. Available data from the pregnancies do not provide a signal of teratogenicity. Study treatment was stopped once the pregnancy was identified. The Maternal Health team reviewed the data submitted by the applicant, summarized below, and concluded the limited cases constituted insufficient information to inform drug associated risk.

**Table 5. Pregnancy Outcome Summary in the plecanatide clinical development program**

	Screening/Placebo	Plecanatide 1 mg	Plecanatide 3 mg	Plecanatide 6 mg
Normal Pregnancy* outcome	4	1	3	4
Pregnancy with unknown outcome (lost to follow up)	0	0	1	3
Spontaneous Abortion	2	0	1	1
Total	6	1	5	8

\*Subject carried pregnancy to term and delivered a healthy baby

Given plecanatide's structural homology to endogenous guanylin/uroguanylin, there is a theoretical concern that there may be a risk of development of guanylin/uroguanylin deficiency if patients develop antidrug antibodies that cross react with endogenous guanylin peptide family members. Adverse events that might suggest this include manifestations of fluid/volume overload (e.g., congestive heart failure, dyspnea, pulmonary congestion, edema, weight increase, blood pressure increase), and hypernatremia. No clear signal of potential guanylin/uroguanylin deficiency adverse events was identified. During the review of the linaclotide NDA review, when the clinical reviewers were considering the potential implications of anti-drug antibodies on endogenous peptides, they found in a literature review that uroguanylin is present in the ductal epithelium of the pancreas and is involved in transfer of fluid into the pancreatic duct. The reviewers considered exocrine pancreatic insufficiency and pancreatitis as potential theoretical manifestations of anti-drug antibody effects in the pancreas. The pancreatitis adverse events in the linaclotide clinical development program were reviewed; there were only two cases, and one was on the placebo arm. The subject who had been treated with linaclotide had a history of chronic pancreatitis. In the current NDA for plecanatide a single pancreatitis SAE was described. That case does not appear to have been a definitively diagnosed as pancreatitis and occurred in a patient with risk factors for pancreatitis, i.e., the patient had a history of gall stones. Post marketing required studies and trials (listed below) will be required as a condition of approval under 505(o) to identify unexpected serious risks related to use of plecanatide in the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and theoretically lead to deficiency syndromes.

The reviewers concluded from their review of the safety database that there was no clear signal of hypersensitivity reactions. A higher number of urticarial events were observed in the plecanatide arms than in placebo; however, the number was very low and when the number of reports of rashes in general were compared, there was no signal. Similarly, the rates of respiratory AEs that may be a manifestation of hypersensitivity were not higher with plecanatide. Another drug in this class, linaclotide, has hypersensitivity reactions listed in the product label. PMR-7 and PMR-13 (listed below) will be conducted to identify the unexpected serious risk of development of immune-mediated reactions with use of plecanatide.

The letter will state the following studies are required:

- |        |   |
|--------|---|
| 3117-7 | Develop and validate a sensitive and precise assay for the detection of anti-plecanatide antibodies (ADA), including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling. |
|--------|---|

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/18

The final report should include screening, confirmation and titer assay validation reports and assay standard operating procedures (SOPs).

3117-8            Develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin.

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/20

The final report should include assay validation reports and the assay standard operating procedures (SOPs).

3117-9            Develop and validate an assay to evaluate the neutralizing capacity of ADAs detected in the patient samples taking Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/20

The final report should include assay validation report and the assay standard operating procedures (SOPs).

In addition, the letter will state that the following trials will be required:

3117-11            Assess development of anti-drug antibody (ADA) responses in patient samples using the immunogenicity serum samples collected in the plecanatide studies (SP304203-00 and SP304203-03 and SP304203-01). Validated assays capable of sensitively and accurately detecting ADA responses, developed under PMR 3117-7, will be used. Evaluate the anti-drug antibody (ADA) rates, individual patient titers and the relationships between ADA status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 04/19

- 3117-12 Use the validated cross reactivity assays developed under PMR 3117-8 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between cross reactivity status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 06/20

- 3117-13 Use the validated neutralizing antibody assay developed under PMR 3117-9 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between neutralizing antibody status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/21

See Sections 4 Nonclinical Pharmacology/Toxicology and 10 Pediatrics of this review for a summary of the pediatric safety issues raised by the lethality observed in the juvenile mice study and the biopsy study that will be required to address this issue under 505(o).

## 9. Advisory Committee Meeting

There was no advisory committee (AC) meeting held to discuss this NDA as there were no issues that required discussion at an AC meeting.

## 10. Pediatrics

See Section 4 Nonclinical Pharmacology/Toxicology of this review regarding the lethality observed in the juvenile animal studies submitted for review. The product label will include a Boxed Warning, Warning and Precaution, and Contraindication addressing pediatric use, which can be found in Section 4 of this review. Section 8.4 Pediatric Use of the product label will present the juvenile animal findings to provide context for the boxed warning and the contraindication. In addition, the label will include a Medication Guide to inform patients of the risk of serious outcomes if plecanatide is administered to pediatric patients.

This application triggers PREA. The applicant revised their previous agreed upon initial Pediatric Study Plan (iPSP) during the review cycle, in response to the PeRC's September 28, 2016 recommendations, in order to align it with the linaclotide's pediatric plan, given that both drugs are in the same class. The plan now includes a partial waiver of pediatric patients less than 2 years of age, given the lethality (deaths due to dehydration within 24 hours of administration) noted in young juvenile mice (corresponding to humans less than 2 years of age; see Section 4 Nonclinical Pharmacology/Toxicology of this review) and the known higher GC-C receptor density in patients less than 2 years of age; there is significant concern that the drug cannot be safely administered in this young age range. Pediatric studies in patients between 2 and <6 years of age will be deferred until the data from a postmarketing required study [under FDAAA 505(o)] to evaluate pediatric GC-C receptor ontogeny are available and have been reviewed. Furthermore, the available pediatric efficacy and safety data from the older pediatric age groups will also be assessed before initiating clinical study in pediatric patients ages 2 to <6 years, assuming the biopsy data support initiating clinical trials in this age group. The biopsy study (and timeline), which the letter will state is required to assess a signal of a serious potential risk of a significant fluid shift into the intestine due to age-dependent expression of the target receptor (GC-C), leading to severe dehydration and possibly death in pediatric patients from birth to 6 years of age exposed to a GC-C receptor agonist, will be identified within the 505(o) section of the approval letter as follows:

3117-10            A study to characterize guanylate cyclase-C (G-CC) mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients ages 0 to 6 years undergoing diagnostic gastrointestinal endoscopies as part of their medical care.

The timetable you submitted on October 13, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	04/19
Final Report Submission	07/19

Pediatric studies in patients ages 6-<18 years will be deferred because the product is ready for approval for use in adults. Pediatric studies in patients ages 2 to <6 years will be deferred because the product is ready for approval for use in adults and the results of the biopsy study and the safety/efficacy/PK results of the dose ranging studies in older patient cohorts are not available for review. The approval letter will describe the studies and a staggered timeline by age group as follows:

3117-1.    Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 12 years to less than 18 years of age by assessing the safety and efficacy of once daily oral plecanatide in an

eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/31/15 (completed)  
Study Completion: 12/18  
Final Report Submission: 02/19

- 3117-2. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 6 years to less than 12 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/18  
Study Completion: 12/20  
Final Report Submission: 02/21

- 3117-3. Confirm the efficacy and safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 years to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12 week treatment study.

Final Protocol Submission: 12/18  
Study Completion: 12/21  
Final Report Submission: 02/22

- 3117-4. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/20  
Study Completion: 12/22  
Final Report Submission: 02/23

3117-5. Confirm the efficacy and safety of Trulance (plecanatide) treatment in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12 week treatment study.

Final Protocol Submission: 12/22  
Study Completion: 12/25  
Final Report Submission: 02/26

3117-6. Assess the long-term safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 18 years of age and have completed a confirmatory efficacy and safety study with plecanatide.

Final Protocol Submission: 02/17  
Study Completion: 06/26  
Final Report Submission: 08/26

Furthermore, given the lethality observed in the juvenile mice studies, there is significant risk to nursing infants if plecanatide or its active metabolite is present in human breast milk. The following trial will be required under 505(o) to identify an unexpected serious risk associated with the presence of plecanatide or its active metabolite in human breast milk:

3117-14 Perform a milk-only lactation trial in lactating women who have received multiple, once daily, doses of Trulance (plecanatide) therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order.

The timetable you submitted on October 13, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/17  
Trial Completion: 06/18  
Final Report Submission: 12/18

Section 8.2 Lactation of the product label will state that there is no information regarding the presence of plecanatide in human milk and that no animal lactation studies of plecanatide have been conducted. The label will note that plecanatide and its metabolite are negligibly systemically absorbed after oral administration, and that it is unknown whether the negligible adult absorption will result in clinically relevant exposures for breastfed infants. Given the latter, this section of the label will also refer to the juvenile animal data in Section 8.4, and state that there is a potential for serious adverse effects to the breastfed infant. The reader will

be advised to consider the developmental and health benefits of breastfeeding along with the mother's clinical need for plecanatide and any potential adverse effects on the breastfed infant from plecanatide or from the underlying maternal condition.

## **11. Other Relevant Regulatory Issues**

OSI – OSI inspected 6 clinical investigator sites, a contract research organization and the sponsor. All inspected received a final classification of voluntary action indicated (VAI) or no action indicated (NAI); however, during the process of site selection OSI noted that two additional clinical investigator sites that had participated in Study SP304203-03 had been classified as Official Action Indicated (OAI) after previous inspections. One site had enrolled 14 subjects and the other had enrolled 16 subjects. OSE recommended removal of the data from these sites as the data was considered unreliable.

Financial disclosure – The Clinical reviewer noted in her review that there were no financial disclosures that caused concern.

## **12. Labeling**

The CDTL has summarized the key labeling issues addressed during the review of this application in her review. I concur with her summary. In addition, see other sections of my review for discussion of labeling issues, including pediatric safety issues addressed in the Contraindication, Boxed Warning, Warning and Precaution 5.1, and Section 8.4 Pediatric Use (see Sections 4 and 10 of this review).

DMEPA - DMEPA found the proposed proprietary name, Trulance, conditionally acceptable. DMEPA considers the name “conditionally acceptable” until approval of the marketing application. DMEPA made recommendations for revisions to the prescribing information, carton labeling and container labels to increase clarity and promote safe use of the product. Those recommendations were incorporated.

OPDP - The recommendations of OPDP were incorporated in labeling

DPMH - The Maternal Health team was consulted and worked with the DGIEP to revise the label to comply with current PLLR regulatory requirements. See also Section 10 Pediatrics of this review regarding how the safety concerns related to exposure of breastfed infants to plecanatide through breast milk were addressed in product labeling.

DMPP – A Medication Guide was considered necessary given the pediatric safety issues associated with plecanatide to inform patients of the risk of serious outcomes if plecanatide is administered to pediatric patients. The DMPP reviewers evaluated the Medication Guide and their recommendations were incorporated.

### 13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies – A REMS was determined to not be necessary to ensure the benefits of plecanatide outweigh the risks. OSE/DRISK was consulted and they concurred with this conclusion. The safety profile of plecanatide is similar to linaclotide, a currently approved GC-C agonist (same drug class). The safety and risk mitigation approach for plecanatide will be similar to other drugs in the class. The risks of plecanatide will be communicated in labeling, which will include a Boxed warning, Contraindication and Warning and Precaution regarding pediatric use, and a Medication Guide.
- Other Postmarketing Requirements and Commitments – See Section 10 Pediatrics above for the PREA requirements associated with the approval of this application. As discussed in Section 10 of this review, a biopsy study to evaluate GC-C receptor ontogeny will be required as a condition of approval, under 505(o). The data from the latter study must be reviewed to assess the safety of initiating pediatric studies in patients ages 2 years to < 6 years of age. The approval letter will state that this study is necessary to assess a signal of a serious risk of a significant fluid shift into the intestine due to age-dependent expression of the target receptor (GC-C), leading to severe dehydration and possibly death, in pediatric patients from birth to 6 years of age exposed to a GC-C receptor agonist.

In addition, the studies and trials listed in Section 8 Safety will be required under 505(o) to identify unexpected serious risks related to use of plecanatide in the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and theoretically lead to deficiency syndromes and to identify an unexpected serious risk of development of immune-mediated reactions with the use of plecanatide.

See Section 10 Pediatrics for a description of the milk-only lactation trial that will be required under 505(o) to identify an unexpected serious risk associated with the presence of plecanatide or its active metabolite in human breast milk.

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/s/  
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DONNA J GRIEBEL  
01/19/2017