CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208745Orig1s000

MEDICAL REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA CONSULT TRACKING NUMBER	AT 2016-046
IND/NDA/BLA NUMBER	NDA 208745
REFERENCED IND FOR NDA/BLA	IND 74883
LETTER DATE/SUBMISSION NUMBER	January 29, 2016/SDN 0
PDUFA GOAL DATE	January 29, 2017
DATE OF CONSULT REQUEST	March 1, 2016
REVIEW DIVISION	Division of Gastroenterology and Inborn Errors Products (DGIEP)
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REVIEW COMPLETION DATE	December 5, 2016
ESTABLISHED NAME/TRADE NAME	Plecanatide/SP-304
APPLICANT	Synergy
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Stool frequency, stool consistency, and straining
COA NAME(S)	Single PRO sign/symptom items
INDICATION	Treatment of chronic idiopathic constipation (CIC) in adult patients
INTENDED POPULATION(S)	Adult patients (18 and 80 years of age, inclusive) meeting the Rome III functional constipation criteria as modified for this study for at least 3 months prior to the Screening visit
PLEASE CHECK ALL THAT APPLY:	☐Rare Disease/Orphan Designation ☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding

(b) (4)

The applicant is currently post-phase 3 in their drug development program and awaiting an approval decision from the FDA. The proposed indication is treatment of chronic idiopathic constipation (CIC) in adult patients.

The applicant proposed single patient-reported outcome (PRO) items in a daily bowel movement (BM) diary assessing for the measurement of completed spontaneous bowel movement (CSBM) and SBM stool frequency, stool consistency, and straining as pre-specified endpoints in two pivotal clinical trials in adult patients (18 and 80 years of age, inclusive) meeting the Rome III functional constipation criteria as modified for this study for at least 3 months prior to the Screening visit.

Although the applicant did not submit a full PRO evidence dossier, based on the all available evidence from the preliminary PRO evidence dossier from the IND phase and the end of phase 2 study (Study 10) data, this review concludes that the PRO instruments used to assess CSBM stool frequency, SBM stool frequency, and stool consistency are fit-for-purpose to support the respective pre-specified secondary endpoints intended for inclusion in labeling claims (see Section C 1.4 [Labeling] for COA Staff modification to applicant's proposed labeling claims) in the context of use. However, the three daily symptom scores (abdominal pain, abdominal discomfort, and abdominal bloating) were not pre-specified in the endpoint testing hierarchy and were not Type I error controlled. This reviewer discussed this with the Clinical review team and these endpoints are not part of the CIC disease definition, therefore, the abdominal symptom instruments were not reviewed for their adequacy to support labeling claims.

With regard to the straining PRO instrument, the applicant modified the response scale, from a 0-10 numeric rating scale to a 5-point verbal response scale, for the final straining scale used in the phase 3 studies. Although the applicant did not submit a full PRO evidence dossier for the final straining instrument, the qualitative patient data generally supported the relevance and meaningfulness of the straining concept and severity. The change from the 0-10 point scale to a 5-point scale does not change the suitability of the straining item to support labeling claims. Based on this reviewer's review of the same five response options used in the 5-point straining

scale from other therapeutic areas and cognitively tested with patients concluding that the response options are generally well-understood and meaningful to patients, with the exception of the "very severe" response option, which some patients believed is redundant and not meaningfully different from "severe."

This reviewer has also reviewed the anchor-based responder definition methods for the pre-specified secondary endpoints. See Section 6 (Interpretation of Scores) below. The COA Staff defer to DGIEP regarding the review of the clinical data to support the pre-specified secondary endpoint labeling claims (i.e., review of the CDF plots showing separation between treatment arms at the meaningful responder thresholds).

This reviewer believes that the four pre-specified secondary endpoints are suitable for inclusion in the label, based on the modest but consistent separation between treatment arms at the meaningful responder thresholds across both studies. See Sections C 1.4 (Labeling), 4 (Content Validity), and 6 (Interpretation of Scores) for further detail.

B. BACKGROUND

Materials reviewed:

- Previous COA Reviews:
  - AT 2011-097; Miskala; finalized in DARRTS on January 13, 2012
  - AT 2010-100; Miskala; finalized in DARRTS on December 29, 2010
- Preliminary PRO evidence dossier from the IND 74883 phase
- End of phase 2 study (Study 10) protocol
- Phase 3 study (Studies 00 and 03) protocols, report bodies, statistical analysis plans
- Applicant's reply to Agency information requests

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

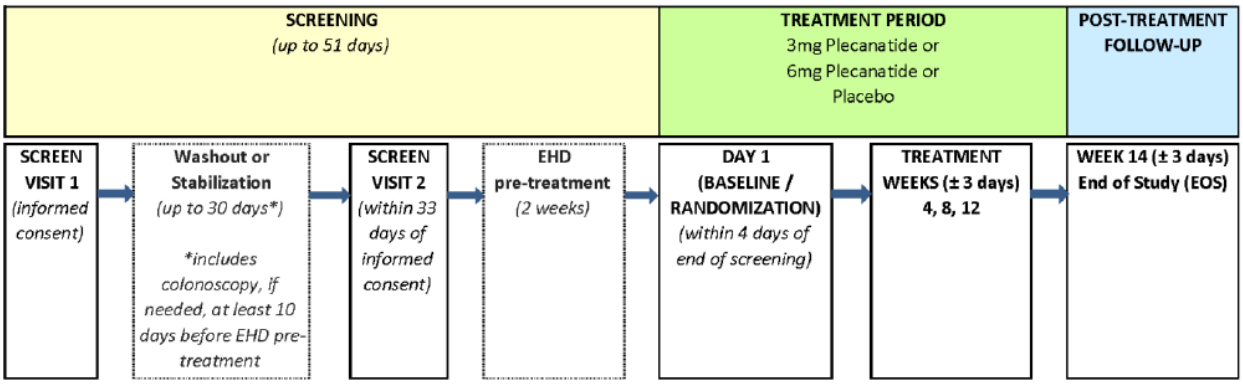
1.1 Clinical Trial Population

Adult patients (18 and 80 years of age, inclusive) meeting the Rome III functional constipation criteria as modified for this study for at least 3 months prior to the Screening visit.

1.2 Clinical Trial Design

Pivotal phase 3 Studies 00 and 03 were both randomized, 12-week, double-blind, placebo-controlled studies to assess the safety and efficacy of plecanatide (3.0 and 6.0 mg) in patients with chronic idiopathic constipation. Both studies included patients from the United States and Canada. The study design of Studies 00 and 03 were identical:

Figure 1: Study Design



1.3 Endpoint Hierarchy and Definition

Concept	Endpoint	Assessment
Primary Endpoint		
Overall CSBM responder	Proportion of patients who are overall CSBM responders during the 12-week Treatment Period. Patients who have ≥3 CSBMs per week and an increase from baseline of ≥1 CSBM for that week. An overall CSBM responder is a patient who is a weekly CSBM responder for at least 9 of the 12 treatment weeks, including at least 3 of the last 4 weeks.	Based on patients' response to the questions regarding number of BMs they experienced in 24 hours, the time of each BM, the completeness of evacuation, and rescue medication use in the Daily BM Diary (see Appendix A).
Secondary Endpoint		
CSBM frequency	Change from baseline over the 12-week treatment period in CSBM frequency rate	Based on patients' response to the questions regarding number of BMs they experienced in 24 hours, the time of each BM, the completeness of evacuation, and rescue medication use in the Daily BM Diary (see Appendix A).
SBM frequency	Change from baseline over the 12-week treatment period in SBM frequency rate	Based on patients' response to the questions regarding number of BMs they experienced in 24 hours, the time of each BM, and rescue medication use in the Daily BM Diary (see Appendix A).

Stool consistency	Change from baseline over the 12-week treatment period in stool consistency score	Based on patients' response to the stool consistency question in the Daily BM Diary (see Appendix A).
Straining	Change from baseline over the 12-week treatment period in straining score	Based on patients' response to the straining question in the Daily BM Diary (see Appendix A).

1.4 Labeling or promotional claim(s) based on the COA

The applicant's targeted labeling claim is:

(b) (4)

Reviewer's comments: Although the applicant did not submit a full PRO evidence dossier, based on the all available evidence from the preliminary PRO evidence dossier from the IND phase and the end of phase 2 study (Study 10) data, this review concludes that the PRO instruments used to assess CSBM stool frequency, SBM stool frequency, and stool consistency are fit-for-purpose to support the respective pre-specified secondary endpoints intended for inclusion in labeling claims in the context of use. This reviewer also believes that the four pre-specified secondary endpoints are suitable for inclusion in the label based on the modest but consistent separation between treatment arms at the meaningful responder thresholds across both studies. See Section 6 (Interpretation of Scores) and Appendices B-H for further detail.

The three daily symptom scores (abdominal pain, abdominal discomfort, and abdominal bloating) were not pre-specified in the endpoint testing hierarchy and were not Type I error controlled; (b) (4) *This reviewer discussed this with the Clinical review team and these endpoints are not part of the CIC disease definition, therefore, the abdominal symptom instruments were not reviewed for their adequacy to support labeling claims.*

The COA Staff defer to DGIEP regarding the review of the clinical data to support the pre-specified secondary endpoint labeling claims (i.e., review of the CDF plots showing separation between treatment arms at the meaningful responder thresholds). Based on the meaningful anchor thresholds derived from the end of phase 2 study (Study 10), this reviewer has concluded the following regarding the first three pre-specified secondary endpoints (see Appendices D-H [CDF plots] and Section 6 [Interpretation of Scores] for further detail). The following findings have been reviewed in collaboration with, and verified by, the Office of Biostatistics review team.

CSBM frequency:

- *There appears to be consistent separation between the 3mg treatment and placebo arm cumulative distribution function (CDF) curves at the meaningful threshold intersection with the x-axis (CSBM frequency endpoint change score) in both Studies 00 and 03.*
- *Study 00 showed about a 19% separation between 3mg and placebo at the 1.8 CSBM threshold (2-point improvement in PGA constipation severity anchor from Study 10).*
- *Study 03 showed about a 12% separation between 3mg and placebo at the 1.8 CSBM threshold (2-point improvement in PGA constipation severity anchor from Study 10).*

SBM frequency:

- *There appears to be consistent separation between the 3mg treatment and placebo arm CDF curves at the meaningful threshold intersection with the x-axis (SBM frequency endpoint change score) in both Studies 00 and 03.*
- *Study 00 showed about a 30% separation between 3mg and placebo at the 2.8 SBM threshold (2-point improvement in PGA constipation severity anchor from Study 10).*
- *Study 03 showed about a 13% separation between 3mg and placebo at the 2.8 SBM threshold (2-point improvement in PGA constipation severity anchor from Study 10).*

Stool consistency:

- *There appears to be consistent separation between the 3mg treatment and placebo arm CDF curves at the meaningful threshold intersection with the x-axis (stool consistency endpoint change score) in both Studies 00 and 03.*
- *Study 00 showed about a 26% separation between 3mg and placebo at the 1.4 stool consistency threshold (2-point improvement in PGA constipation severity anchor from Study 10).*
- *Study 03 showed about a 24% separation between 3mg and placebo at the 1.4 stool consistency threshold (2-point improvement in PGA constipation severity anchor from Study 10).*

With regard to straining, the fourth pre-specified secondary endpoint, this reviewer has concluded the following (see Appendices E-H [CDF plots]):

Straining:

- *It is important to note that the applicant did not conduct cognitive interviews with CIC patients to support the 5-point straining item and response options that were used in the two phase 3 studies. However, the same five response options used in the 5-point straining scale have been used in other therapeutic areas and cognitively tested with patients concluding that the response options are generally well-understood and meaningful to patients, with the exception of the "very severe" response option, which some patients believe is redundant and not meaningfully different from "severe."*

- *The applicant did, however, conduct cognitive testing of a 0-10 point numeric rating straining scale and interviewed patients regarding their definition of severe straining. See Section 4 (Content Validity) for how patients, who reported experiencing severe or very severe straining, defined severe straining.*

- *The 5-point straining scale was not included in the end of phase 2 Study 10 (an 11-point numeric rating scale [NRS] for straining was included, rather than the 5-point straining scale that was used in the phase 3 trials, Studies 00 and 03); therefore, the Study 10 anchor scales could not be used to establish a responder definition.*
  - *However, based on examining cross-validation anchor thresholds (obtained from one phase 3 study and applied to the other), it appears that the 2-point improvement in PGA constipation severity anchor is meaningful to patients and corresponded with about a 1-point improvement in straining score (i.e., matching up with a -1.1 point straining score change in Study 00 and a -0.9 point straining score change in Study 03 at the median score on the PGA constipation severity anchor scale):*
  - *The improvement threshold of a 1-point improvement in straining score showed a separation between 3mg treatment and placebo arms of about 15% in Study 00 and 13% in Study 03.*
- *Based on qualitative research with patients in other disease areas, a one-point improvement from "very severe" to "severe" may not be a meaningful improvement for patients. That said, there were approximately 10% of patients in both studies in both the 3mg and placebo arms who reported that they were experiencing "very severe" straining at baseline. See applicant's response below to FDA's information request for the baseline severity of straining from both phase 3 studies:*

Table 1
Baseline Straining
SP304203-00
ITT Population

Baseline Straining	Placebo (N=452)	3 mg Plecanatide (N=453)	6 mg Plecanatide (N=441)
Very Severe	40 (9.0%)	42 (9.5%)	48 (11.2%)
Severe	154 (34.6%)	147 (33.3%)	136 (31.9%)
Not Severe	251 (56.4%)	252 (57.1%)	243 (56.9%)

Table 2
Baseline Straining
SP304203-03
ITT Population

Baseline Straining	Placebo (N=445)	3 mg Plecanatide (N=443)	6 mg Plecanatide (N=449)
Very Severe	45 (10.3%)	45 (10.3%)	61 (13.8%)
Severe	172 (39.5%)	200 (45.7%)	177 (40.0%)
Not Severe	218 (50.1%)	193 (44.1%)	204 (46.2%)

- *See "Reviewer's comments" in Section 4 (Content Validity) and 6 (Interpretation of Scores) for more information regarding the straining endpoint.*
- *If straining is accepted into the label, this reviewer recommends that the following language is used: "amount of straining with bowel movements (amount of time pushing or physical effort to pass stool)." This language is in line with the Linzess CIC labeling language for straining and is in line with the way patients (from the qualitative one-on-one interviews) interpreted severe straining (see Section 4 [Content Validity] for further detail).*

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The applicant did not provide a conceptual framework for the single-item sign and symptom scales.

3 CLINICAL OUTCOME ASSESSMENTS

The applicant had patients complete the constipation sign and symptom endpoint questions in the daily BM diary via electronic handheld device in both their phase 3 pivotal studies (Study 00 and Study 03). The questions were related to complete spontaneous bowel movement (CSBM), rescue medication use, SBM frequency, stool consistency, straining, and abdominal symptoms (Appendix A).

The patients completed the daily BM diary at least once daily, following the Schedule of Assessments table below reproduced from the applicant's Study 00 protocol:

Table 2: Schedule of Assessments

Study Period	Screening[a]		Treatment				Post Treatment	
Visit	Screening-1	Screening-2 Pre treatment	Week 1	Week 4	Week 8	Week 12 (EOT)	Week 14 (EOS)	Early Withdrawal
Visit (Window) Days	0 to 4 weeks Start Pre-Treatment		Day 1 within 4 days of end of Screening Period	Day 28±3	Day 56±3	Day 84±3	2 weeks after DOPV (± 3)	within 5 days of withdrawal
Informed Consent	X							
Inclusion/Exclusion Criteria	X		X					
Medical History (GI and Bowel Habits)/Demographics	X		X					
Colonoscopy[b]	X							
Prior and Concomitant Medications/Diet	X		X	X	X	X	X	X
Physical Examination[c]	X		X	X	X	X	X	X
Vital Signs[d]	X		X	X	X	X	X	X
Pregnancy Test[e]	X	X	X			X	X	X
Serum Chemistry, Hematology, Urinalysis[f]	X		X	X	X	X	X	X
Immunogenicity serum testing[g]			X	X			X	X
Urine Drug Screen[h]	X	X	X					
12-Lead Electrocardiogram[i]	X		X			X		X
Train on EHD/Review response[j]	X	X	X	X	X	X		
Randomization			X					
Study Drug Administration[k]			X					
Study Drug Dispensed[l]			X	X	X			
Study Drug Collection and Accountability				X	X	X	X	X
Rescue Med Supply/Resupply[m]	X		X	X	X	X		
Daily BM and Symptom Diaries (EHD)[n]	X	X	X	X	X	X	X	X
PAC-QoL, PAC-SYM, PGA Questionnaires[o]			X	X	X	X	X	X
Adverse Events[p]	X	X	X	X	X	X	X	X

NA = not applicable; EOT = End of Treatment; EOS = End of Study; DOPV = day of previous visit; EHD = Electronic Hand-held Device; CIC = Chromic Idiopathic Constipation; PAC = Patient Assessment of Constipation; QoL = Quality of Life; SYM = symptom; PGA = Patient Global Assessment

The applicant did not submit a full PRO evidence dossier with the NDA and replied to the Agency's request for a full evidence dossier by acknowledging their risk in opting not to provide one. The Agency's request sent on March 16, 2016 was as follows:

> **Submit a patient-reported outcome (PRO) evidence dossier supporting the PRO instruments that you included as key secondary endpoints proposed for inclusion in labeling (i.e., measuring "straining," (b) (4) (b) (4)). The PRO evidence dossier should include the following:**
>
> - **Documentation of content validity of the PRO instruments, including a qualitative research report summarizing any literature reviews, expert interviews, research conducted with patients showing support that the core symptoms being measured are relevant and meaningful to CIC patients, that patients had defined the PRO items/questions and response options consistently (e.g., did the definitions of**

(b) (4) overlap?), and that patients understood the items and response options in the way they were intended

- **Exact copies of the PRO instruments in the format that they were administered to patients in your phase 3 trials (e.g., paper versions, electronic screen shots), along with any user manuals and any training materials for the site, investigator, and patient**
- **Psychometric analysis report including measurement properties of the PRO instruments (i.e., reliability, validity, ability to detect change) based on the longitudinal phase 3 data**
- **PRO endpoint scoring algorithms**
- **Clinically meaningful responder definitions for the PRO endpoints, including anchor-based analyses conducted with phase 3 data to establish clinically meaningful change from baseline for the PRO endpoints, using the two Patient Global Assessment (PGA) questions (change in constipation and constipation severity)**
- **Cumulative distribution function (CDF) plots for the two PGA anchor scales that you plan to use to support the responder definitions you are proposing for the PRO endpoints**

Reviewer's comments: This reviewer went back to the qualitative data submitted by the applicant during the IND 74883 phase and reviewed those preliminary data during the NDA review. With regard to the straining PRO instrument, the applicant modified the response scale, from a 0-10 numeric rating scale to a 5-point verbal response scale, for the final straining scale used in the phase 3 studies. Although the applicant did not submit a full PRO evidence dossier for the final straining instrument, the qualitative patient data generally supported the relevance and meaningfulness of the straining concept and severity. The change from the 0-10 point scale to a 5-point scale does not change the suitability of the straining item to support labeling claims. Based on this reviewer's review of the same five response options used in the 5-point straining scale from other therapeutic areas and cognitively tested with patients concluding that the response options are generally well-understood and meaningful to patients, with the exception of the "very severe" response option, which some patients believed is redundant and not meaningfully different from "severe."

With regard to scoring of the first four pre-specified endpoints (CSBM frequency, SBM frequency, stool consistency, and straining), the applicant stated the following reproduced from the Study 00 protocol:

8.8.2 Secondary Efficacy Endpoints

For the following key secondary efficacy endpoints, each plecanatide dose will be compared to placebo using the appropriate statistical methodology defined below.

8.8.2.1 Change From Baseline over the 12-week Treatment Period in CSBM Frequency Rate

The change from baseline in the number of CSBMs over the 12-week treatment period will be computed into weekly rates based on the mean replacement approach as defined in Section 8.4 and will be analyzed using a linear mixed-effects model with fixed effects for gender (stratification variable), treatment, week, the interaction of treatment and week and the corresponding baseline value and random intercept for patient. A Least Square (LS) mean with 95% confidence intervals and the corresponding statistical p-value will be presented for each week and across the 12 week time-period for the difference between each plecanatide group and placebo. The key secondary endpoint will be based on the LS mean overall average estimate across the 12-week treatment period.

8.8.2.2 Change from Baseline over the 12-week Treatment Period in SBM Frequency Rate

The change from baseline in the number of SBMs over the 12-week treatment period will be computed into weekly rates based on the mean replacement approach as defined in Section 8.4 and will be analyzed using a linear mixed-effects model with fixed effects for gender (stratification variable), treatment, week, the interaction of treatment and week and the corresponding baseline value and random intercept for patient. A Least square (LS) mean with 95% confidence intervals and the corresponding statistical p-value will be presented for each week and across the 12 week time-period for the difference between each plecanatide group and placebo. The key secondary endpoint will be based on the LS mean overall average estimate across the 12-week treatment period.

8.8.2.3 Change From Baseline over the 12-week Treatment Period in Stool Consistency Score

The change from baseline in the stool consistency score (i.e., BSFS) over the 12-week treatment period will be computed into average weekly scores based on the mean replacement approach as defined in Section 8.4, and will be analyzed using a linear mixed-effects model with fixed effects for gender (stratification variable), treatment, week, the interaction of treatment and week and the corresponding baseline value and random intercept for patient. A Least square (LS) mean with 95% confidence intervals and the corresponding statistical p-value will be presented for each week and across the 12 week time-period for the difference between each plecanatide group and placebo. The key secondary endpoint will be based on the LS mean overall average estimate across the 12-week treatment period.

8.8.2.4 Change From Baseline over the 12-week Treatment Period in Straining Score

The change from baseline in the straining score over the 12-week treatment period will be computed into average weekly scores based on the mean replacement approach as defined in Section 8.4, and will be analyzed using a linear mixed-effects model with fixed effects for gender (stratification variable), treatment, week, the interaction of treatment and week and the corresponding baseline value and random intercept for patient. A Least square (LS) mean with 95% confidence intervals and the corresponding statistical p-value will be presented for each week and across the 12 week time-period for the difference between each plecanatide group and placebo. The key secondary endpoint will be based on the LS mean overall average estimate across the 12-week treatment period.

With regard to the applicant's plans for handling missing data, the applicant stated the following reproduced from their statistical analysis plan for Study 00:

4.1.2 Missing Data Conventions

In general, data will not be imputed for safety analyses.

For the responder analyses, patients who have fewer than four complete diary days will be considered "non-responders" for that week. For this indication (CIC) the diary is considered complete for the day if the patient has made at least one Daily BM Diary entry, including rescue medication use, or Daily Symptom Diary entry. If a patient has between 4 and 6 days of assessments (inclusive) in a week, the calculations will be based on a mean replacement approach (MRA). Using MRA, when diary data are missing in a week with partial data, the calculation of the overall weekly CSBM / SBM rate during a given week is 7 times the number of CSBMs / SBMs divided by the number of days the patient reported bowel habits data. Where, in the following sections of this document, reference is made to employing a linear mixed-effects model for assessing change from baseline, or an analysis of covariance (ANCOVA) is specified, patients with no assessments in a week will be left as missing in these models.

For secondary efficacy endpoints based on the change from baseline, a mean replacement approach (MRA) will be applied to missing data. Specifically, for BMs, when diary data are missing in a week with partial data, the calculation of the overall weekly CSBM / SBM rate during a given week is 7 times the number of CSBMs / SBMs divided by the number of days the patient reported bowel habits data; however, if a patient has less than 4 days of diary entries in a week, the entire week will be set to missing. For stool consistency and straining scores, any missing diary entry in a week does not contribute to either the numerator or denominator in computing the average score for the week, i.e., the weekly scores equal the total of the BSFS or straining scores reported for the week divided by the number of scores reported for that week; however, if a patient has less than 4 days of diary entries in a week, the entire week will be set to missing for the BSFS or straining score. Patients with no assessments in a week will be left as missing in the linear mixed model (i.e., missing weekly data will not be imputed) under the assumption that the weekly data is missing-at-random (MAR).

To assess the robustness of the study conclusions to choice of missing data methodology, sensitivity analyses will be performed for imputing missing weekly data using multiple imputation (MI) and last observation carried forward (LOCF). Additional sensitivity analyses may be performed to test the assumption that missing weekly data are MAR.

In addition, a summary of change from baseline in certain BM efficacy variables will be presented employing observed case (OC) methodology. For OC, any missing diary entry in a week with partial data will be assigned as no bowel movement.

Patients with no assessments in a week will be left as missing in any linear mixed model or CMH efficacy analyses.

4 CONTENT VALIDITY

The applicant conducted qualitative research with patients in the United States (see previous COA review: AT 2011-097; Miskala; finalized in DARRTS on January 13, 2012).

- Phase 1 concept elicitation interviews were conducted in 20 patients with CIC (meeting either a two-seven of the Rome III Part C criteria) in 4 waves of individual one-on-one interviews with 5 patients each). Interviews lasted approximately 60 minutes. Cognitive interviews were conducted with an additional 15 patients with CIC (meeting either a four-seven of the Rome III Part C criteria) in 2 waves of interviews.
- Phase 2 cognitive interviews were conducted in 15 patients with CIC (meeting either a four or five of the Rome III Part C criteria) completed at three clinical sites in the US. Interviews were completed in 3 waves of interviews.

To date, the following information has been submitted (check all that apply):

☒Literature review and/or publications
☒Documentation of expert input

☒Qualitative study protocols and interview guides for focus group or patient interviews
☒Chronology of events for item generation, modification, and finalization (item tracking matrix)
☒Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
☒Qualitative support for meaningful change
☒Quantitative study summary with evidence to support item retention and scoring
☐Transcripts (if available)

The applicant concluded that the results from the concept elicitation and cognitive interviews supported the modification and finalization of the daily BM diary scales to include the severity of the most predominant, important, and bothersome symptoms of CIC, as well as the use of clear terminology for the items, response options, and recall periods for the daily BM diary and the patient global anchor scales.

It is important to note that the 5-point straining scale that was used in the two phase 3 studies (Studies 00 and 03) was not cognitively debriefed with patients; only the 11-point numeric rating scale version of the straining item was tested with patients.

Worthy of mention is the way the interviewed patients defined severe straining. Based on the patients' quotes included in the applicant's qualitative study reports submitted during the IND 74883 phase, this reviewer had some concern that the patients might be defining severe straining in different ways. Therefore, the following information request was sent to the applicant on October 7, 2016:

> Using data from the CIC patients participating in the 50 qualitative interviews (phases 1 and 2 of the qualitative interviews during IND 74883), provide a table displaying the patients' interpretation of severity of straining. The table should include one row per patient with information included in four columns:
>
> a. An "X" in either Column 1 or Column 2, or another interpretation of severe straining in Column 3:
>   i. Column 1: Patient defined severity of straining as amount of time or effort spent pushing/forcing a bowel movement
>   ii. Column 2: Patient defined severity of straining as straining that causes rectal pain, bleeding, tearing, or hemorrhoids
>   iii. Column 3: A description of another interpretation of severity of straining that does not fit into Column 1 or 2
> b. A description of how the patient describes his/her own current level of straining severity (e.g., none, mild, moderate, severe, very severe) in Column 4.

The following clarification to the information request was sent to the applicant on October 27, 2016:

> Submit an updated table that does not treat Columns 1 and 2 as mutually exclusive. Place an "X" in both Columns 1 and 2 if patients defined straining in both ways during their interviews.

The applicant's response to the information requests resulted in the following calculations by this reviewer:

- Of the 32 patients (of the 50 interviewed) who defined severe straining during their interviews:
    - 60% (n=19/32) defined severe straining as amount of time or effort spent pushing/forcing a bowel movement
    - 40% (n=14/32) defined severe straining as straining that causes rectal pain, bleeding, tearing, or hemorrhoids

- Of the 18 CIC patients that reported that they are currently experiencing severe straining (i.e., at least reporting a 6 on the 0-10 point straining scale or reporting "severe" or "very severe" straining):
    - 83% (n=15/18) defined severe straining as amount of time or effort spent pushing/forcing a bowel movement
    - 61% (n-11/18) defined severe straining as straining that causes rectal pain, bleeding, tearing, or hemorrhoids
        - Of those 11 patients, 73% (n=8/11) also defined straining as amount of time or effort spent pushing/forcing a bowel movement.

Therefore, it appears that most of the patients defined severe straining as amount of time or effort spent pushing/forcing a bowel movement, regardless of whether or not they also defined it as causing rectal pain, bleeding, tearing, or hemorrhoids.

See Section 6 (Interpretation of Scores) for further detail on patients' impressions regarding the patient global anchor scales.

Reviewer's comments: The applicant opted not to provide a full PRO evidence dossier with their NDA submission in response to FDA's information request for the full dossier sent on March 16, 2016; the applicant also acknowledged that they were aware of the risk in not providing a full dossier for Agency review. Nonetheless, the applicant did provide a preliminary PRO evidence dossier during the IND 74883 phase (including patient qualitative interview reports and item tracking matrices). The qualitative work conducted did include cognitive testing of the exact scales used for the first three secondary endpoints (CSBM frequency, SBM frequency, and stool consistency). However, all patient qualitative work was done with an 11-point NRS straining instrument, not the 5-point straining scale that was used in the phase 3 trials. The applicant modified the response scale, from a 0-10 numeric rating scale to a 5-point verbal response scale, for the final straining scale used in the phase 3 studies. Although the applicant did not submit a full PRO evidence dossier for the final straining instrument, the qualitative patient data

generally supported the relevance and meaningfulness of the straining concept and severity. The change from the 0-10 point scale to a 5-point scale does not change the suitability of the straining item to support labeling claims. Based on this reviewer's review of the same five response options used in the 5-point straining scale from other therapeutic areas and cognitively tested with patients concluding that the response options are generally well-understood and meaningful to patients, with the exception of the "very severe" response option, which some patients believed is redundant and not meaningfully different from "severe."

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

This reviewer could not find results from any psychometric properties and performance analyses that might have been conducted by the applicant. The applicant opted not to submit a full PRO evidence dossier to support the reliability, validity, and ability to detect change for the pre-specified endpoints.

6 INTERPRETATION OF SCORES

The applicant tested a number of different improvement/change anchor scales within their patient cognitive debriefing one-on-one interviews. This reviewer has included a brief summary below of the relevant findings concerning the two anchor scales that were used to interpret the meaningfulness of the statistically significant improvement findings in the endpoint scores from the patients' perspective. The applicant did not submit patient interview transcripts; therefore, the information below is based on the applicant's cognitive interview reports that included some patient quotes.

Patient Global Assessment (PGA) Constipation Severity (Appendix B)

- The PGA Constipation Severity item is a current state anchor scale) with no risk of recall error.
- This item was used by this reviewer as the primary anchor scale to establish the meaningfulness of improvement in patient scores over time (week 12 score minus baseline score.
- The applicant did not ask patients what would be meaningful to them regarding a one-, two-, or three-category change in response options over time for this item.
  Reviewer's comments: Given that more than one patient (phase 1, wave 2) implied that a change from "very severe" to "severe" might not be a meaningful improvement (one patient quote was: "severe and very severe to me would be pretty much the same), this reviewer considered a two-category change as a meaningful improvement anchor.

Patient Global Assessment (PGA) Constipation Change (Appendix C)

- The PGA Constipation Change item required patient recall from the start of study medication 12 weeks earlier; some patients expressed being unable to recall back that far; risk of recall error
    - Some patients (phase 2, waves 1 and 3) expressed having difficulty remembering signs and symptoms even from three days earlier (some patient quotes regarding being able to remember back three days were: "that would be hard for me," "possibly not," "now you are getting a little bit foggy," "that is when it is hard to remember," "no," "that is still a little tougher") and some stated that they would need to consult a log or documentation to be able to address a lengthy recall period.
- Some patients (phase 2, waves 1, 2, and 3) felt that the response option "minimally improved" is not meaningful (some patient quotes were: "from really bad to minimal would not mean very much," "not too much change," "it didn't help much," "you would have some change for the better, but not very much," "you notice some change, just not a whole lot of change," "it is a slight change," "it would mean that it is kind of working, but not really doing the job that I would think").
- However, the response options "much improved" and "very much improved" appeared to be meaningful to patients in terms of adequate improvement in constipation symptoms.
  Reviewer's comments: For the reasons stated above, the PGA Constipation Change item was not used by this reviewer as the primary anchor scale. The response options of "much improved" and "very much improved" were used to support the meaningfulness findings based on the PGA Constipation Severity anchor scale.

The following information request was sent to the applicant on July 11, 2016:

> For the following analyses, please remove the data from patients enrolled at the two [problematic] sites noted above.
>
> Note: for the requested graphs below, specify the number of subjects included in each cumulative distribution function (CDF) curve in the graph legend, e.g. -1 point change (n=33).
>
> 1. Provide cumulative distribution function (CDF) plots using the PGA constipation severity item and PGA constipation change item to aid in determining clinically meaningful change from baseline in the following sign/symptom secondary endpoint scores:
>   - CSBM stool frequency
>   - SBM stool frequency
>   - Stool consistency
>   - Straining
> 2. Provide the following eight CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):

- CDF plot of pooled treatment and placebo group data with PGA constipation severity baseline to Week 12 change score curves (i.e., -1 point change, -2 point change, -3 point change, -4 point change, no change, +1 point change) with sign/symptom change score on x-axis

3. Provide the following eight CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):
    - CDF plot of pooled treatment and placebo group data with PGA constipation severity baseline to overall average of 12 weeks change score curves (i.e., -1 point change, -2 point change, -3 point change, -4 point change, no change, +1 point change) with sign/symptom change score on x-axis
4. Provide the following eight of CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):
    - CDF plot of pooled treatment and placebo group data with PGA constipation change Week 12 curves (i.e., very much improved, much improved, minimally improved, no change, and minimally worse) with sign/symptom change score on x-axis
5. Provide the following eight CDF plots (i.e., separate plots for each of the four secondary endpoints listed above, as well as separately for each clinical trial):
    - Separate curves for the treatment versus placebo groups with sign/symptom change score on x-axis.
6. Provide the following Spearman correlations and scatterplots separately for each clinical trial:
    - Each of the four secondary endpoint change scores with the baseline to Week 12 PGA constipation severity change scores
    - Each of the four secondary endpoint change scores with the baseline to overall average of 12 weeks PGA constipation severity change scores
    - Each of the four secondary endpoint change scores with the Week 12 PGA constipation change scores

On August 17, 2016, the following information request was sent to the applicant:

1) In reference to the July 11, 2016 information request (IR) sent by FDA for CDF plots from the two pivotal phase 3 trials:
    a. Provide the median change scores (50% percentile) corresponding to each PGA constipation change category/curve (i.e., very much improved, much improved, minimally improved, no change, and minimally worse) and PGA constipation severity point change category/curve (i.e., -1 point change, -2 point change, -3 point change, -4 point change, no change, +1 point change) for each of your CDF plots (i.e., CSBM stool frequency, SBM stool frequency, stool consistency, and straining) you submitted in response to the July 11, 2016 IR.
2) Confirm that the bowel movement CIC Diary questions assessing the frequency and completeness of BMs that you included in the end of phase 2 psychometric evaluation study (Study 10) were identical to those included as the first three key secondary endpoints (CSBM stool frequency, SBM stool frequency, and stool consistency) in the two phase 3 trials (Studies 00 and 03), and that calculation of the first three key secondary endpoints was done in the same way as was done the phase 3 trials. We noted that the straining items are not identical across the studies; therefore, the following IR does not apply to the straining question in Study 10.

3) If the BM CIC diary questions and endpoint scores included in Study 10 match up identically with the questions/scores used to assess the three key secondary endpoints in Studies 00 and 03, treat your 24-hour PGA constipation severity question and PGA constipation change question as anchor scales using your Study 10 data to conduct the following post-hoc analyses:

   Note: for the requested graphs below, specify the number of subjects included in each CDF curve in the graph legend, e.g. -1 point change (n=33).

   a. Provide CDF plots using the PGA constipation severity item and PGA constipation change item to aid in determining clinically meaningful change from baseline in the Study 10 items that match up identically with the first three secondary endpoint items:
      - CSBM stool frequency
      - SBM stool frequency
      - Stool consistency

   b. Provide the following six CDF plots (i.e., separate plots for each of the three secondary endpoints listed above):
      - CDF plot of pooled treatment and placebo group data with PGA constipation severity baseline to Week 12 change score curves (i.e., -1 point change, -2 point change, -3 point change, -4 point change, no change, +1 point change) with endpoint change score on x-axis
      - CDF plot of pooled treatment and placebo group data with PGA constipation severity baseline to overall average of 12 weeks change score curves (i.e., -1 point change, -2 point change, -3 point change, -4 point change, no change, +1 point change) with endpoint change score on x-axis

   c. Provide the following six CDF plots (i.e., separate plots for each of the three secondary endpoints listed above):
      - CDF plot of pooled treatment and placebo group data with PGA constipation change Week 12 curves (i.e., very much improved, much improved, minimally improved, no change, and minimally worse) with endpoint change score on x-axis

   d. Provide the following three CDF plots (i.e., separate plots for each of the three secondary endpoints listed above, as well as separately for each clinical trial):
      - Separate curves for the treatment versus placebo groups with endpoint change score on x-axis.

   e. Provide the following Spearman correlations and scatterplots:
      - Each of the first three secondary endpoint change scores with the baseline to Week 12 PGA constipation severity change scores
      - Each of the first three secondary endpoint change scores with the baseline to overall average of 12 weeks PGA constipation severity change scores
      - Each of the first three secondary endpoint change scores with the Week 12 PGA constipation change scores

On November 16, 2016, the following information request was sent to the applicant:

> Rerun the following eight CDF plots (see list below for exact figure numbers from your CDF submission dated September 23, 2016) by including separate curves for the 3mg dose, 6mg dose, and placebo arms (include the sample sizes for each curve) and strictly following the missing data plan you specified in your statistical analysis plans for each of the endpoints below (e.g., "if a patient has less than 4 diary entries in a week, the entire week will be set to missing."):
>
> 1. Figure 4.4.1 (CSBM stool frequency averaged over 12 weeks by treatment; Study 00)
> 2. Figure 4.4.2 (SBM stool frequency averaged over 12 weeks by treatment; Study 00)
> 3. Figure 4.4.3 (Stool consistency averaged over 12 weeks by treatment; Study 00)
> 4. Figure 4.4.4 (Straining averaged over 12 weeks by treatment; Study 00)
> 5. Figure 4.5.1 (CSBM stool frequency averaged over 12 weeks by treatment; Study 03)
> 6. Figure 4.5.2 (SBM stool frequency averaged over 12 weeks by treatment; Study 03)
> 7. Figure 4.5.3 (Stool consistency averaged over 12 weeks by treatment; Study 03)
> 8. Figure 4.5.4 (Straining averaged over 12 weeks by treatment; Study 03)

Reviewer's comments: It is important to note that the 5-point straining scale was not included in the end of phase 2 Study 10 (an 11-point NRS for straining was included, rather than the 5-point straining scale that was used in the phase 3 trials, Studies 00 and 03); therefore, the Study 10 anchor scales could not be used to establish a responder definition. Rather, this reviewer had to cross-validate the responder definition using anchor scales from Study 00 and applying them to Study 03 and vice versa to see if there was consistency across the two phase 3 studies. Both phase 3 studies' anchor scales pointed to a one-point improvement in straining as being a meaningful change.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Not applicable given that both pivotal phase 3 studies were conducted in the United States and Canada.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

9 REVIEW USER MANUAL

Not provided by applicant.

APPENDIX A – DAILY BM DIARY

Appendix 5 Electronic Hand-Held Device Questions

Daily Bowel Movement Diary

- Confirm you would like to report a Bowel Movement that occurred today. (Yes / No)
- Please record the time that this Bowel Movement occurred today.
- Did you feel like you completely emptied your bowels during this Bowel Movement? (Yes / No)
- Select the picture most resembling your stool. [Bristol Stool Form Scale graphic shows on screen]
- Please remember to tell the [device name] each time you have a Bowel Movement.
- Please remember that even if you enter bowel movements or rescue medication use during the day you still need to complete Daily Symptom Diary in the evening every day.

Rescue Medication Usage

- Confirm you are ready to take Dulcolax® now. (Yes / No / Already Taken)
- On the following screens, please review the Rescue Medication (Dulcolax®) entries you have made in the [device name] so far today.
- You recorded taking Dulcolax® at the following time(s) today: [DAY] [Time] [Number of pills]
- Do you still need to record a time that you took Dulcolax® today? (Yes / No)
- Please record the time that you took your Dulcolax® today.
- Enter the number of pills you took at this time.
- Please remember to tell the [device name] each time you take your Dulcolax®.

Daily Symptom Diary

The patient will be asked to rate their symptoms using their EHD.

This questionnaire should be answered each day during the Daily Symptom Diary completed in the evening. There is not an option to enter data from a previous day in this study.

- The Daily Symptom Diary begins now…
- You will enter your response on a scale of 0 to 4, where 0 is none , 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe.
- 1. Abdominal Bloating. For today, rate your abdominal bloating at its worst on a scale of 0 to 4.
- 2. Abdominal Discomfort. For today, rate your abdominal discomfort at its worst on a scale of 0 to 4.
- 3. Abdominal Pain. For today, rate your abdominal pain at its worst on a scale of 0 to 4.
- Today, did you have a bowel movement? (Yes / No)
- 4. Straining. For today, when you had a bowel movement, rate your straining at its worst on a scale of 0 to 4.

APPENDIX B – PGA CONSTIPATION SEVERITY SCALE

Constipation Severity

How would you rate the severity of your constipation at its worst in the past 24 hours?

- 1= none
- 2 = mild
- 3 = moderate
- 4 = severe
- 5 = very severe

APPENDIX C – PGA CONSTIPATION CHANGE SCALE

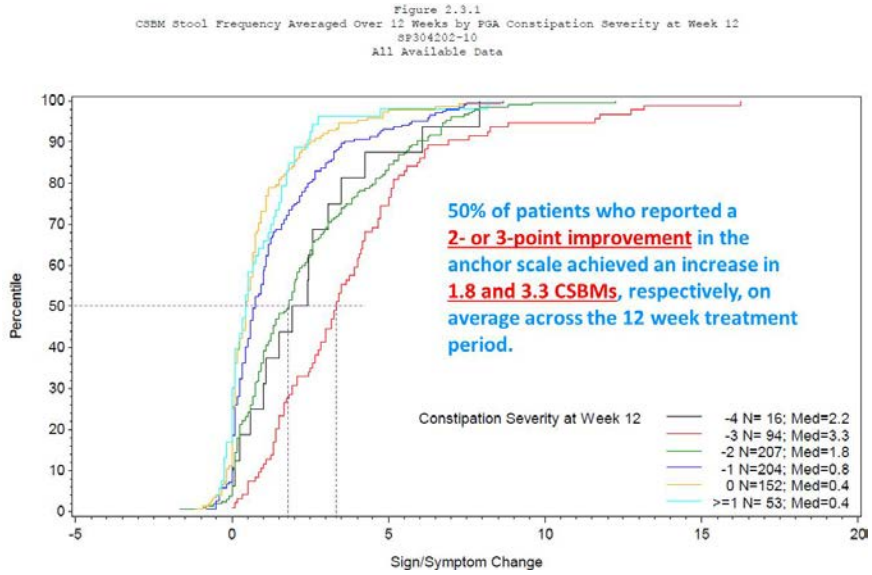
Change in Constipation

Since the time you first started taking study medication, how would you describe the change (if any) in your constipation?

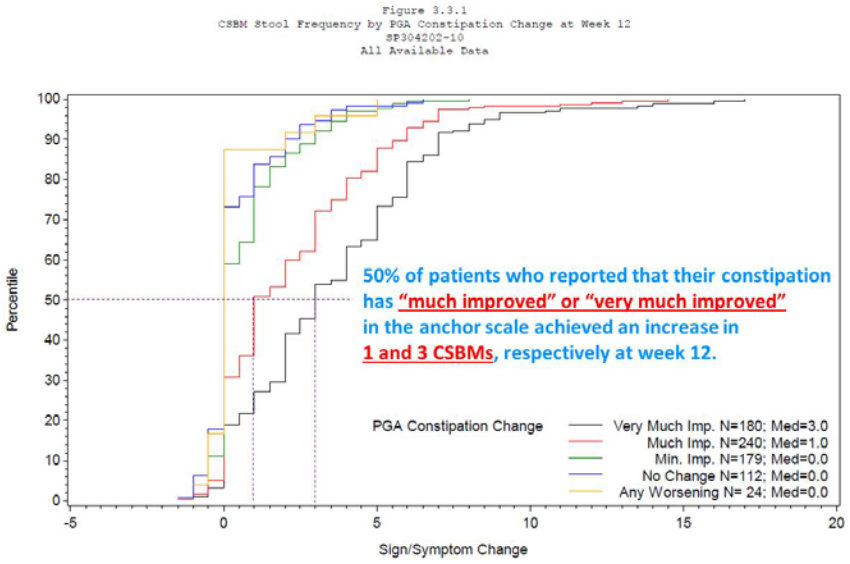
- o 1 = very much improved
- o 2 = much improved
- o 3 = minimally improved
- o 4 = no change
- o 5 = minimally worse
- o 6 = much worse
- o 7 = very much worse

APPENDIX D – CDF PLOTS (EOP2 STUDY 10 ANCHOR SCALES FOR FIRST THREE PRE-SPECIFIED SECONDARY ENDPOINTS)

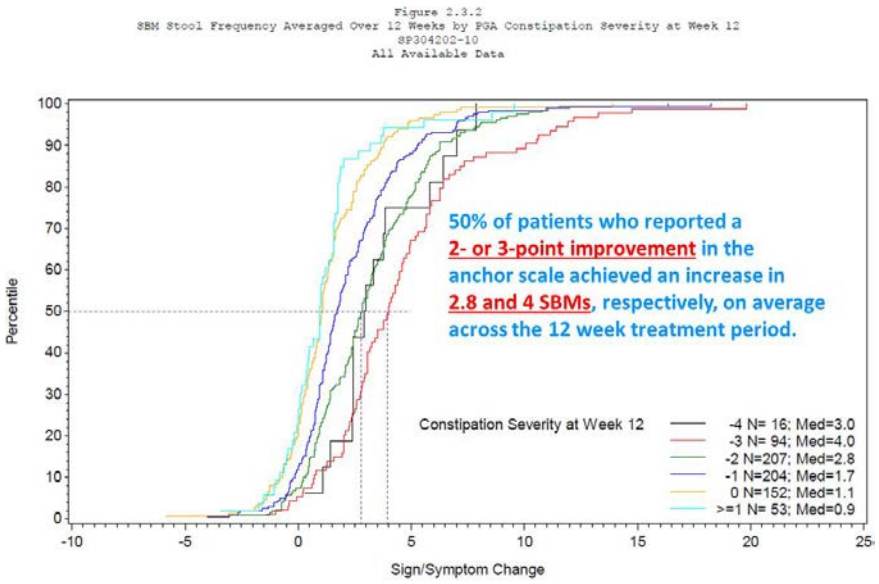
CSBM Frequency <u>overall 12-week change</u> by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (EOP2 Study 10)



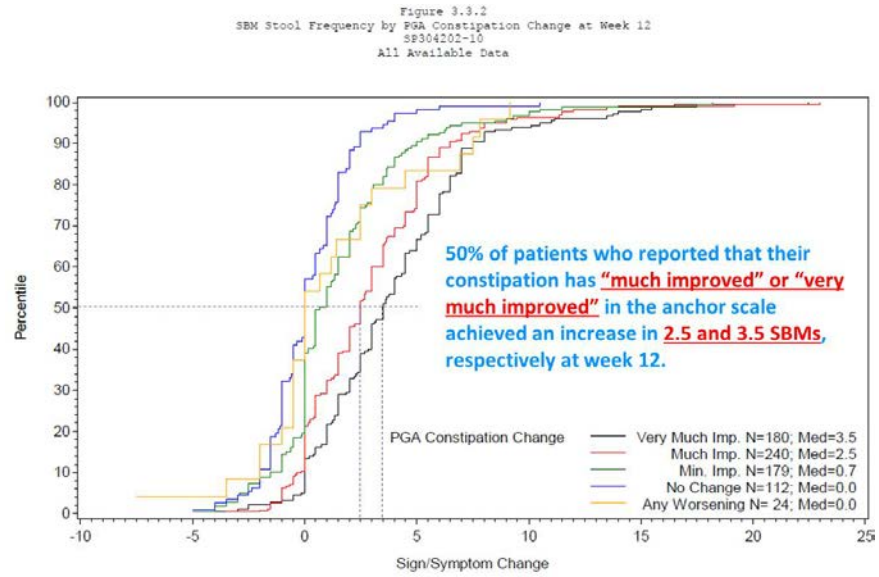
CSBM Frequency <u>change at Week 12</u> by PGA Constipation Change anchor scale (EOP2 Study 10)



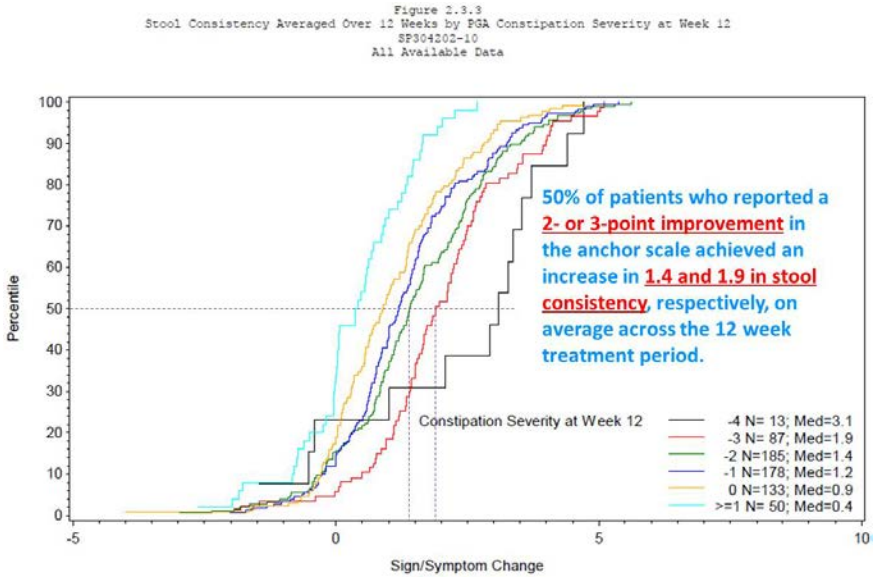
SBM Frequency <u>overall 12-week change</u> by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (EOP2 Study 10)



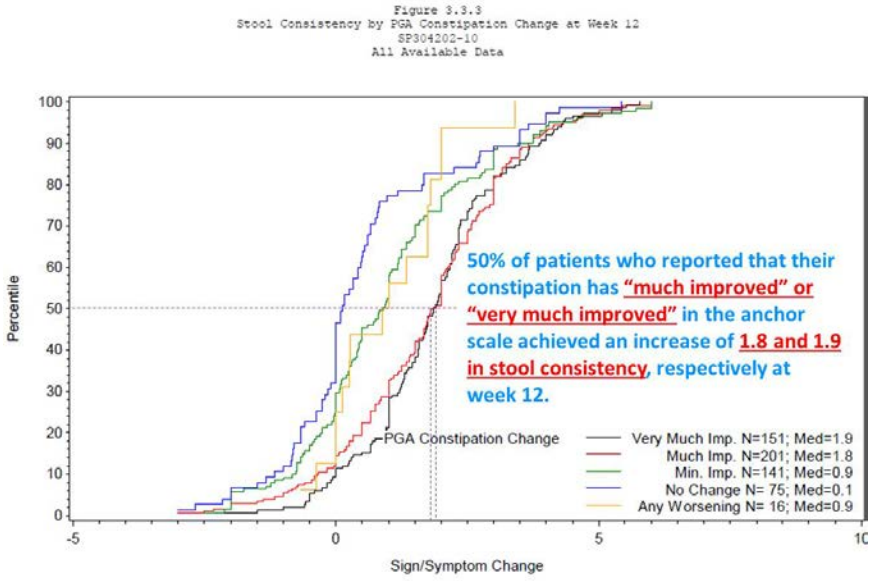
SBM Frequency <u>change at Week 12</u> by PGA Constipation Change anchor scale (EOP2 Study 10)



Stool Consistency <u>overall 12-week change</u> by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (EOP2 Study 10)

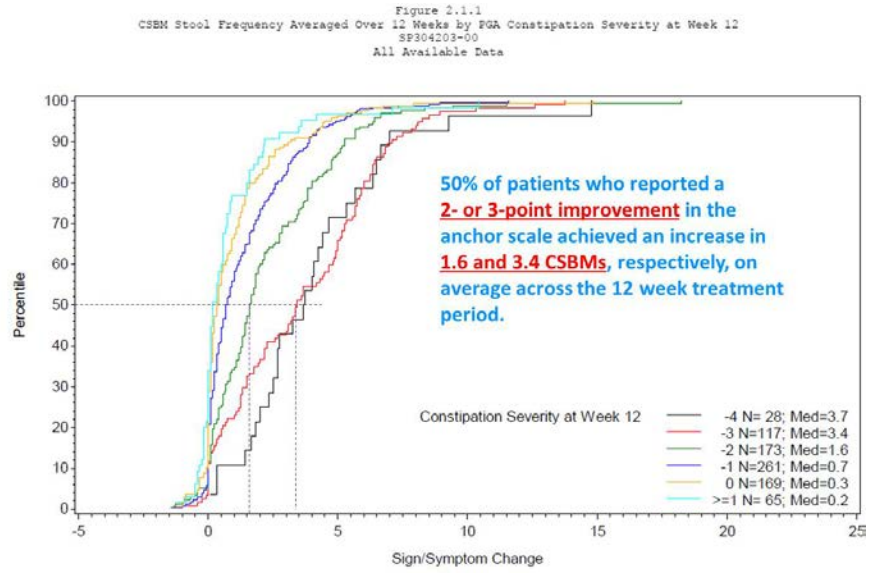


Stool Consistency <u>change at Week 12</u> by PGA Constipation Change anchor scale (EOP2 Study 10)

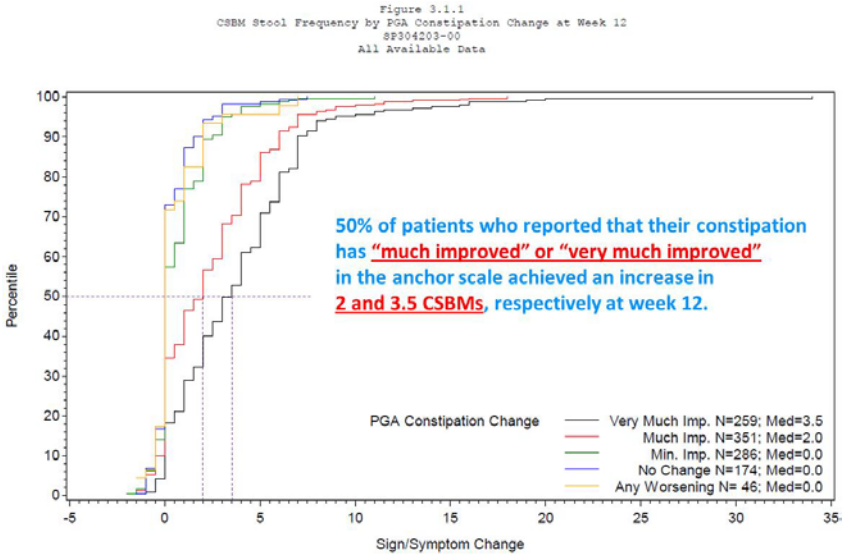


APPENDIX E – CDF PLOTS (STUDY 00 ANCHOR SCALES FOR FIRST FOUR PRE-SPECIFIED SECONDARY ENDPOINTS)

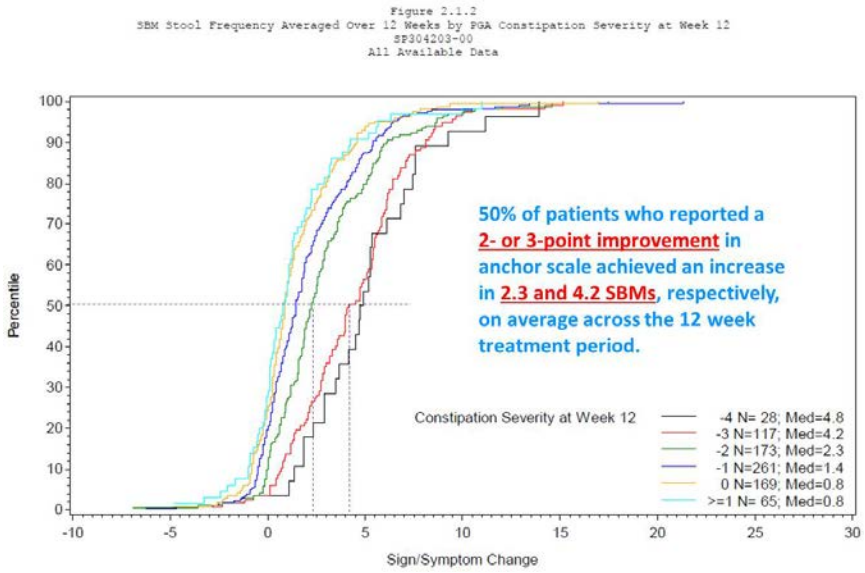
CSBM Frequency overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 00 for confirmation)



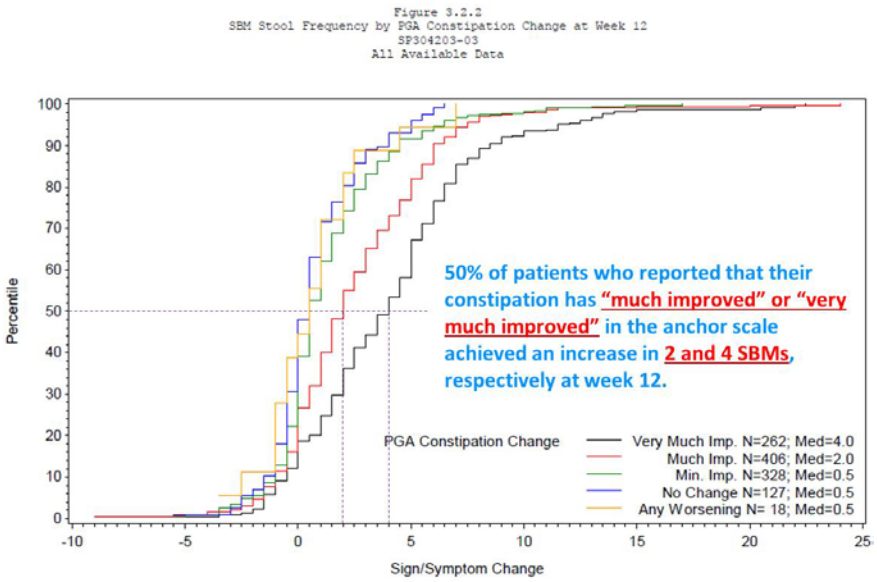
CSBM Frequency change at Week 12 by PGA Constipation Change Anchor (Study 00 for confirmation)



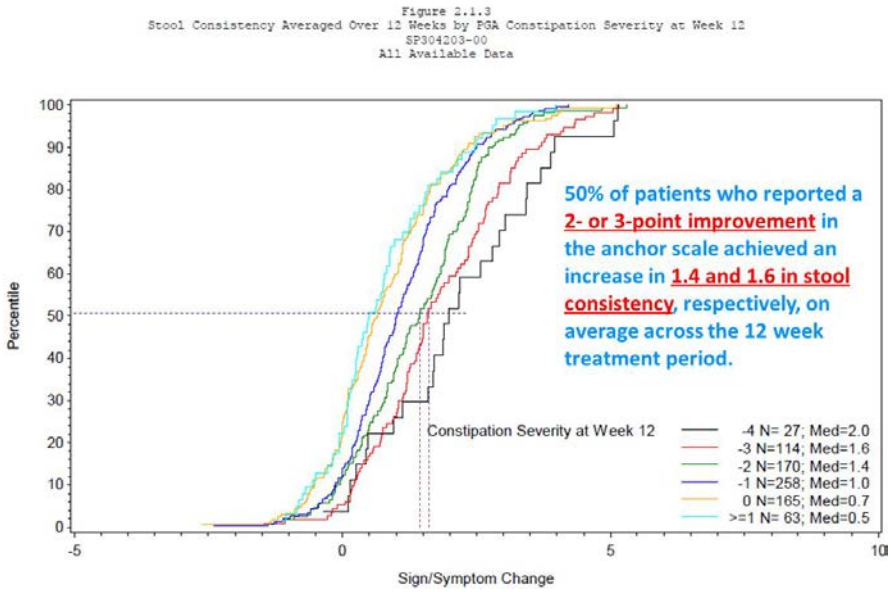
SBM Frequency overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 00 for confirmation)



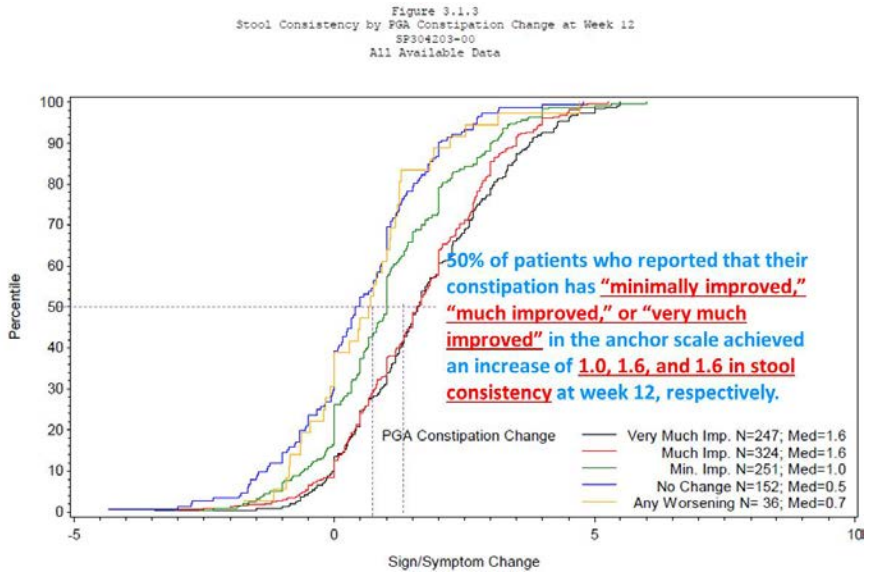
SBM Frequency change at Week 12 by PGA Constipation Change Anchor (Study 00 for confirmation)



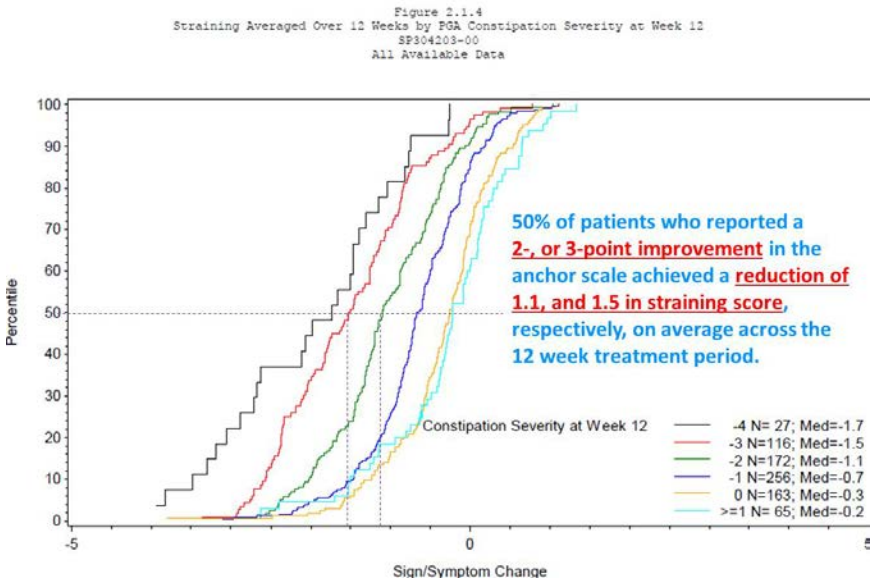
Stool Consistency overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 00 for confirmation)



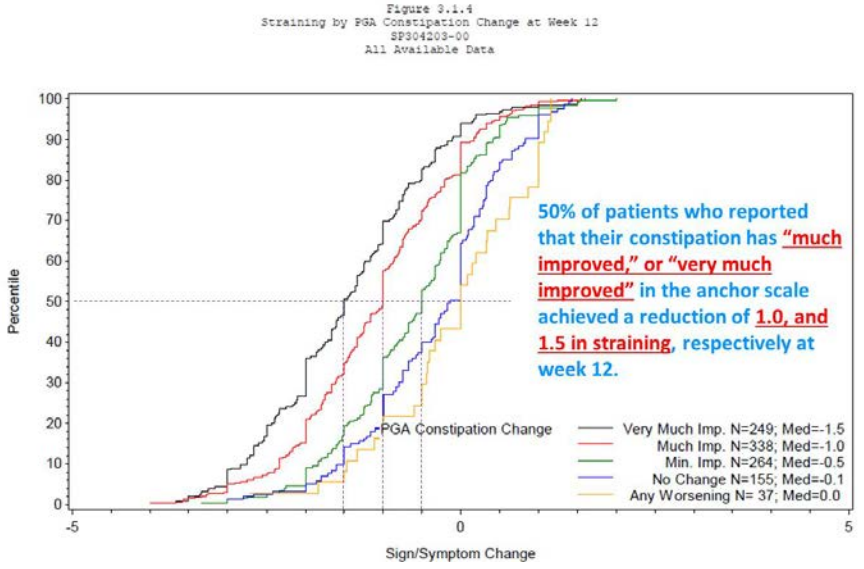
Stool Consistency change at Week 12 by PGA Constipation Change Anchor (Study 00 for confirmation)



Straining overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 00)

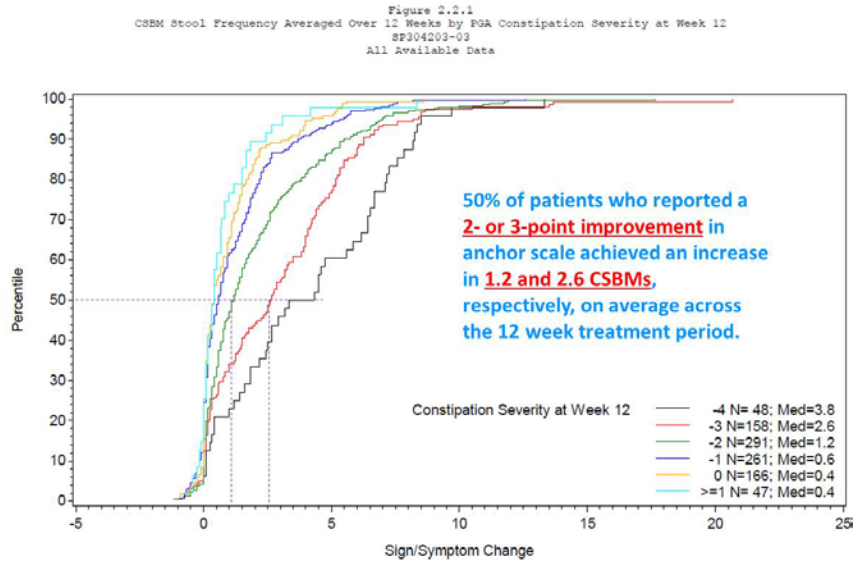


Straining change at Week 12 by PGA Constipation Change Anchor (Study 00)

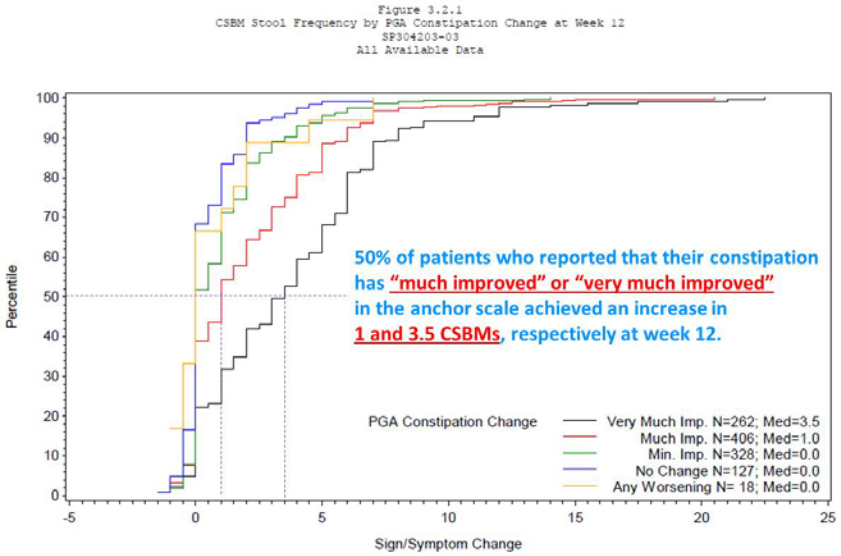


APPENDIX F – CDF PLOTS (STUDY 03 ANCHOR SCALES FOR FIRST FOUR PRE-SPECIFIED SECONDARY ENDPOINTS)

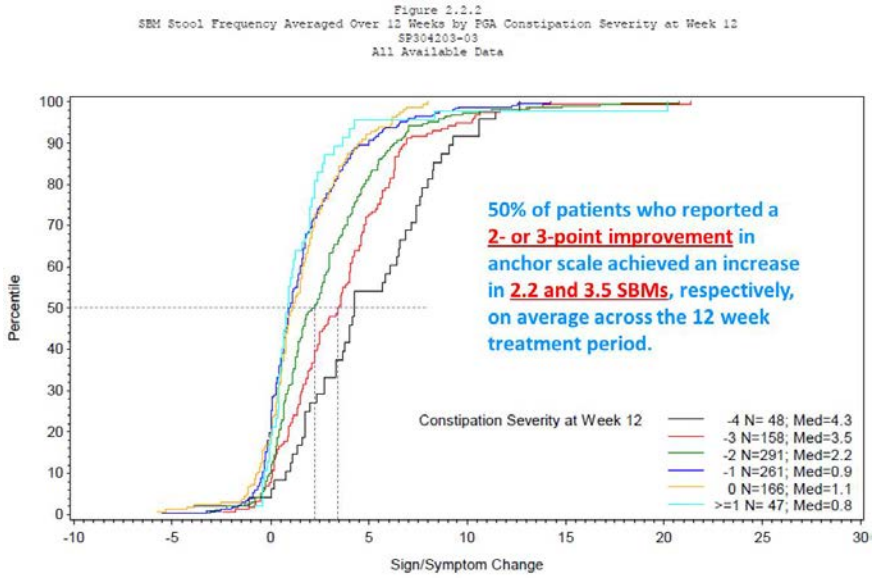
CSBM Frequency overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 03 for confirmation)



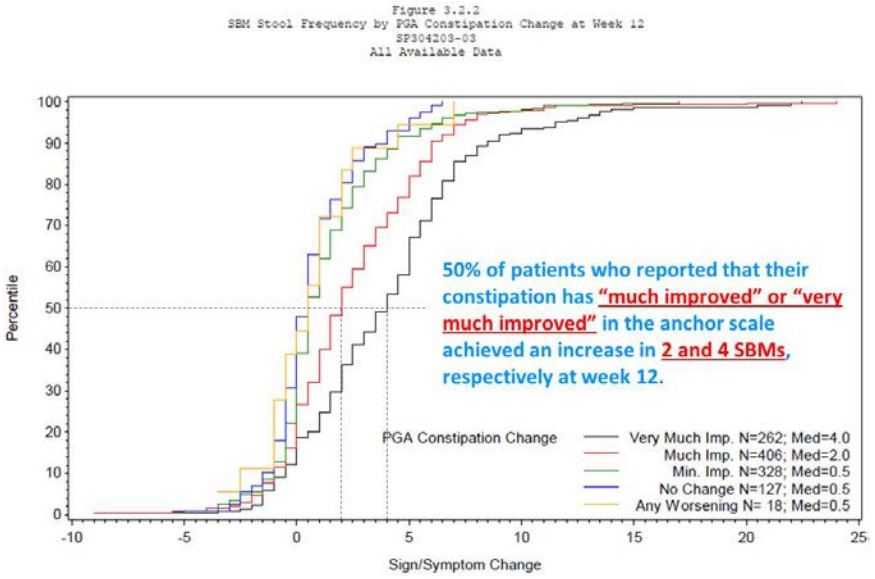
CSBM Frequency change at Week 12 by PGA Constipation Change Anchor (Study 03 for confirmation)



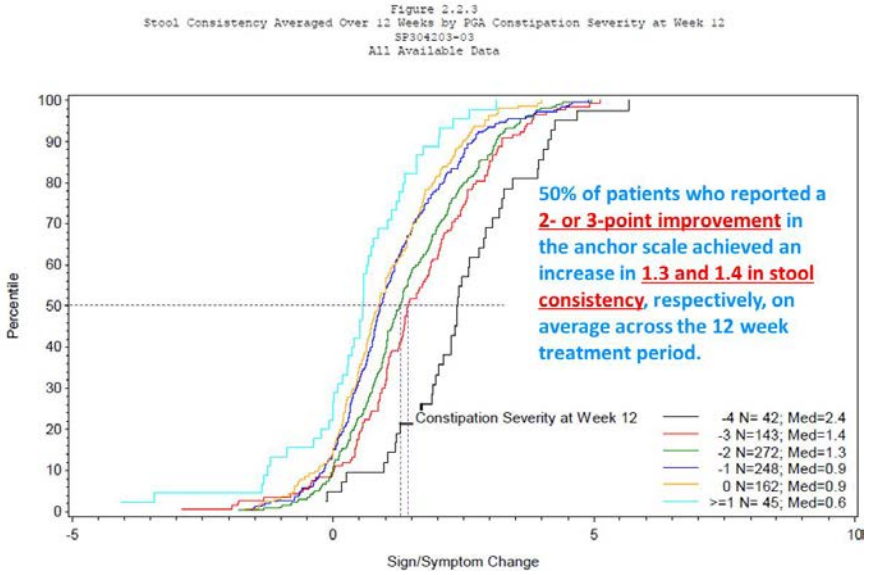
SBM Frequency overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 03 for confirmation)



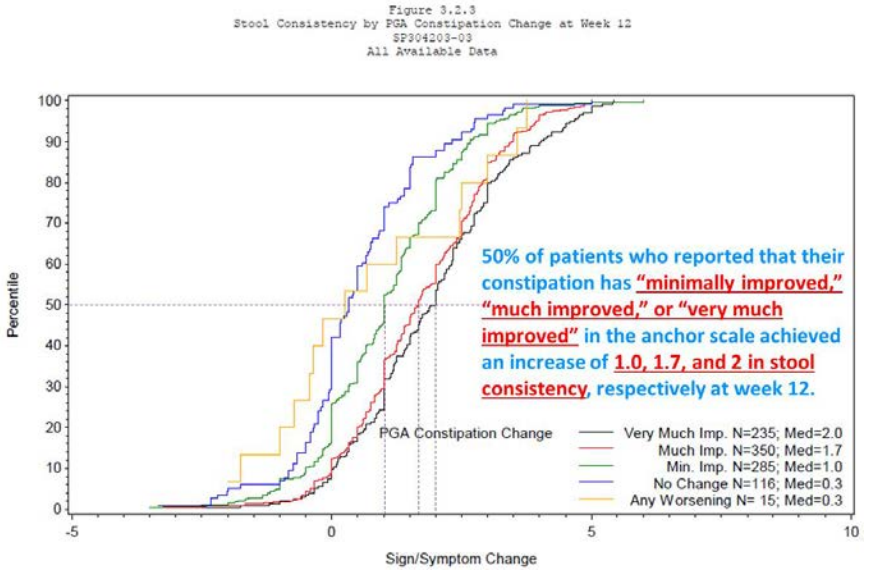
SBM Frequency change at Week 12 by PGA Constipation Change Anchor (Study 03 for confirmation)



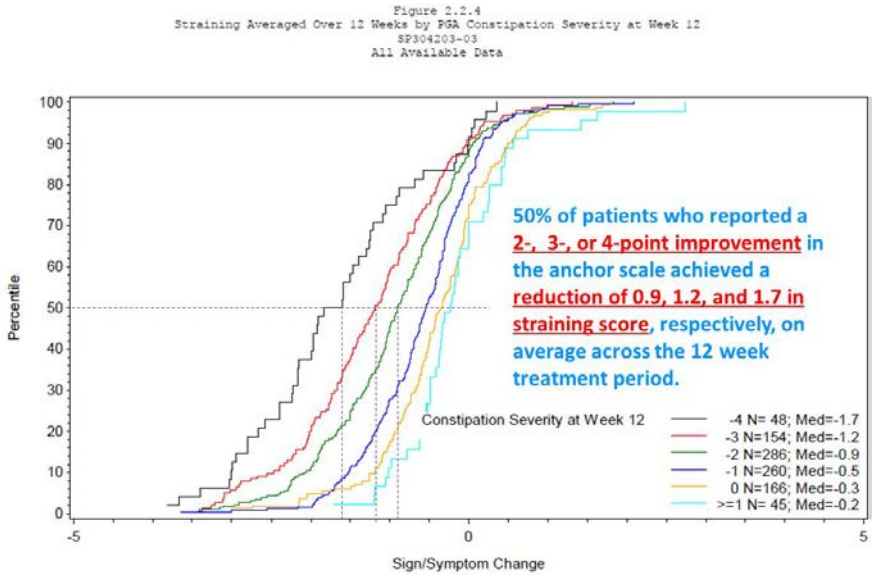
Stool Consistency overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 03 for confirmation)



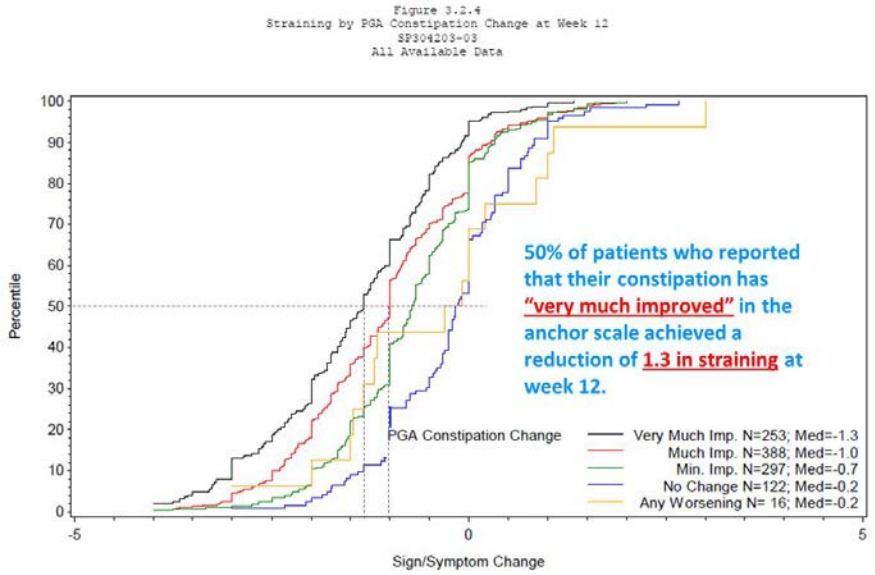
Stool Consistency change at Week 12 by PGA Constipation Change Anchor (Study 03 for confirmation)



Straining overall 12 week change by PGA Constipation Severity anchor scale (week 12 score minus baseline score) (Study 03)

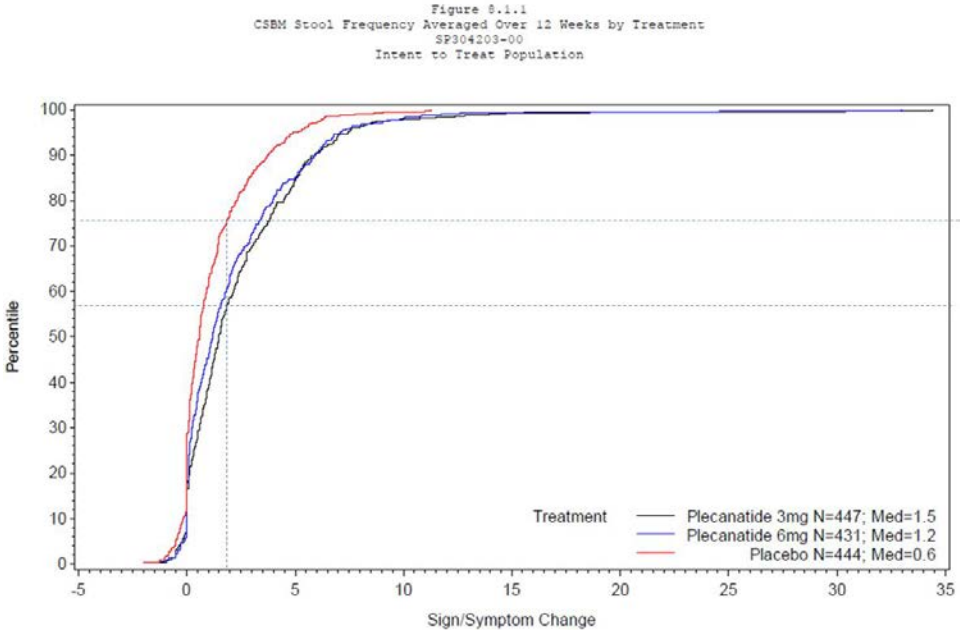


Straining change at Week 12 by PGA Constipation Change Anchor (Study 03)

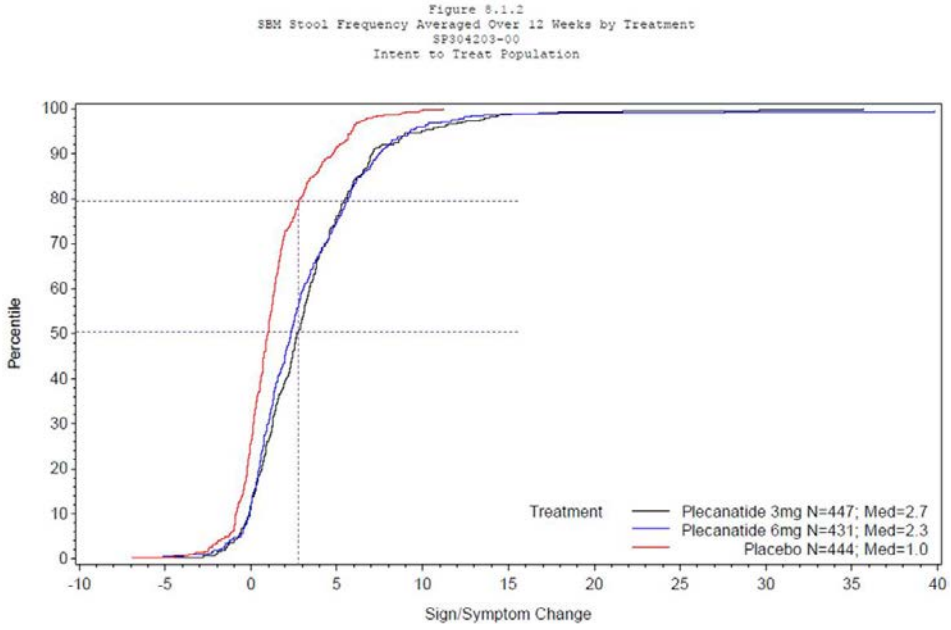


APPENDIX G – CDF PLOTS (STUDY 00 TREATMENT VERSUS PLACEBO CURVES FOR FIRST FOUR PRE-SPECIFIED SECONDARY ENDPOINTS)

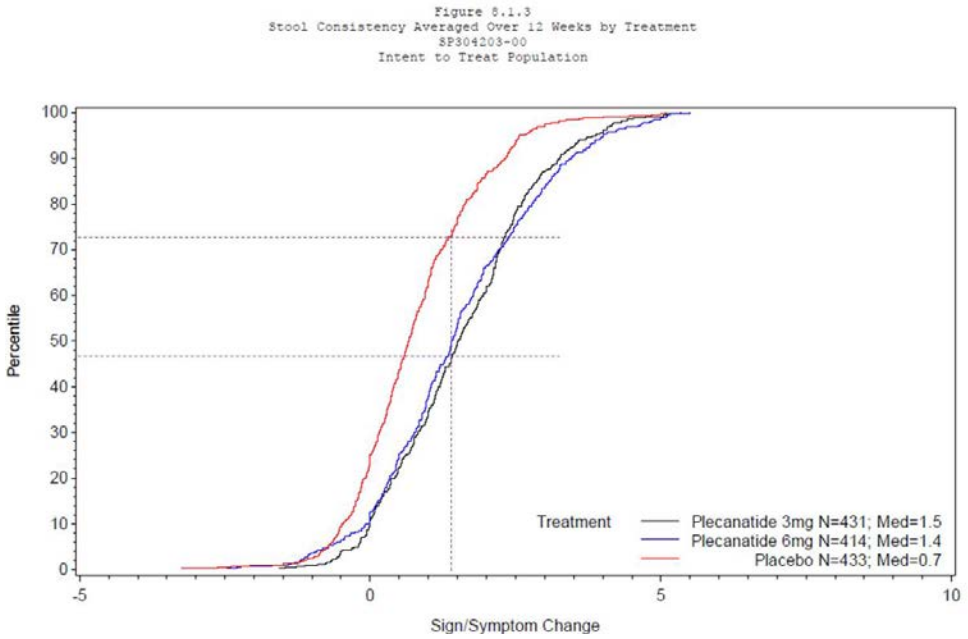
CSBM Frequency overall 12 week change by Treatment Group (Study 00)



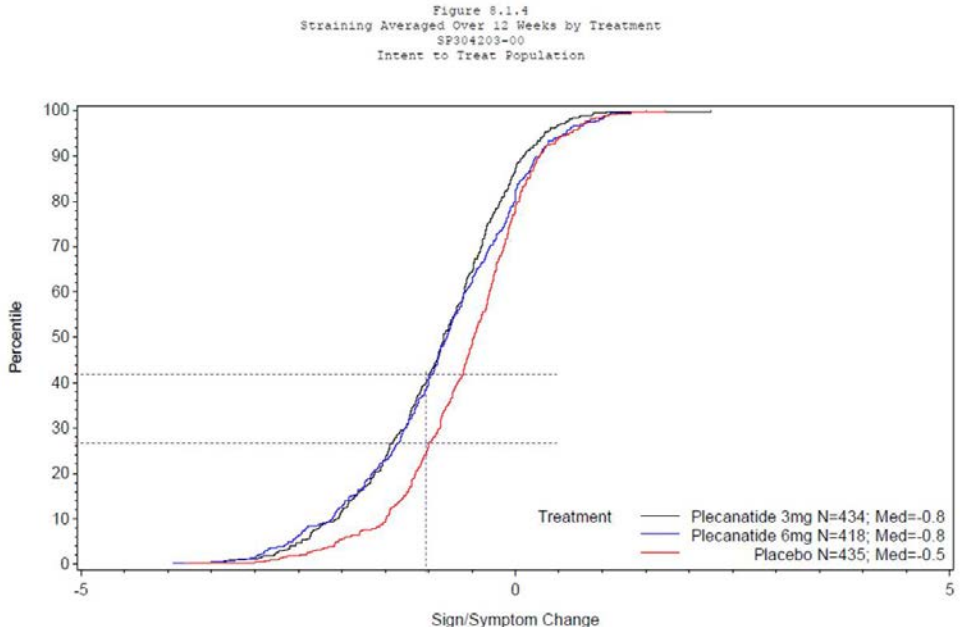
SBM Frequency overall 12 week change by Treatment Group (Study 00)



Stool Consistency overall 12 week change by Treatment Group (Study 00)

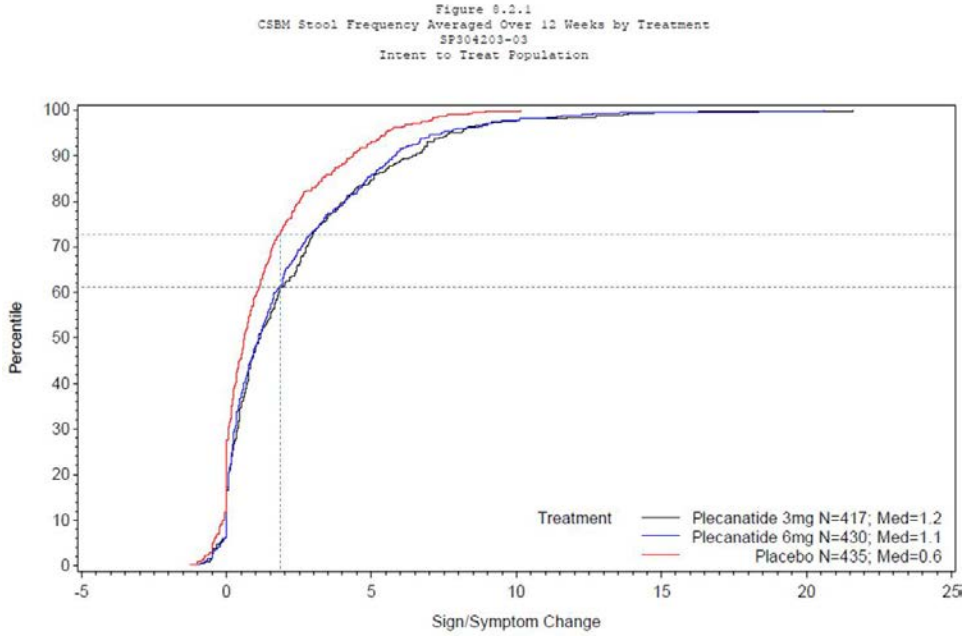


Straining overall 12 week change by Treatment Group (Study 00)

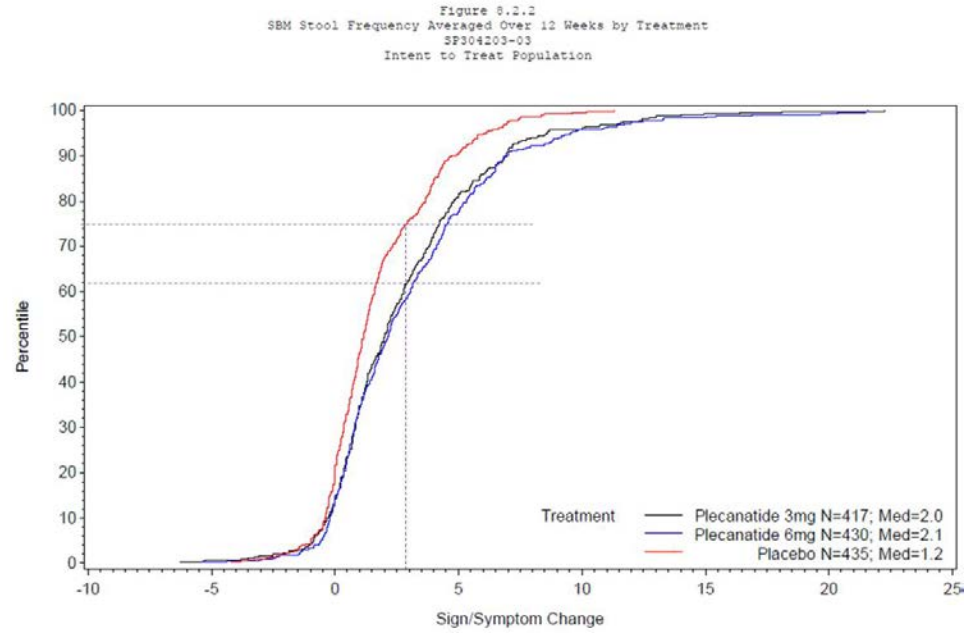


APPENDIX H – CDF PLOTS (STUDY 03 TREATMENT VERSUS PLACEBO CURVES FOR FIRST FOUR PRE-SPECIFIED SECONDARY ENDPOINTS)

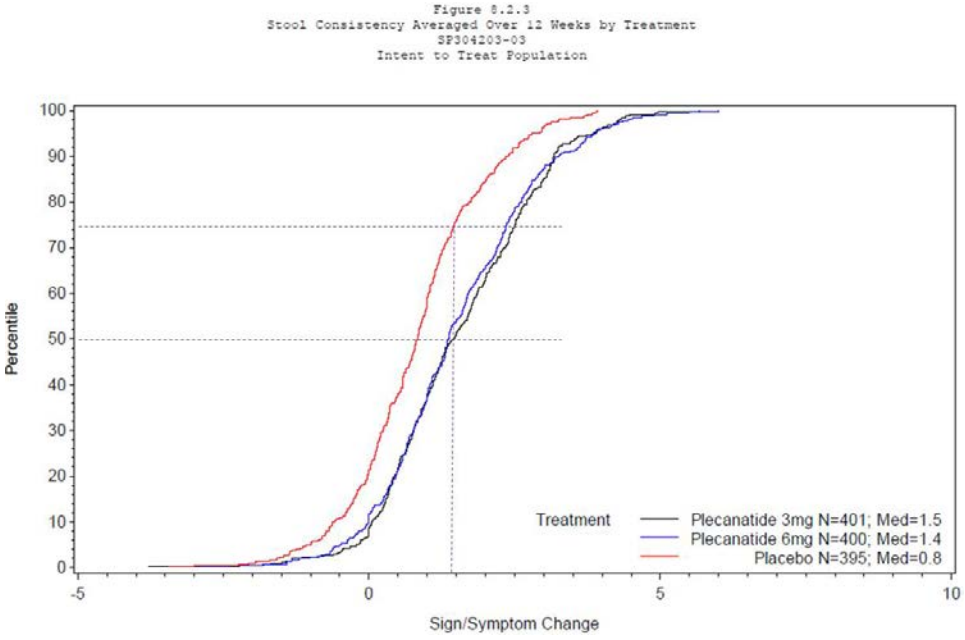
CSBM Frequency overall 12 week change by Treatment Group (Study 03)



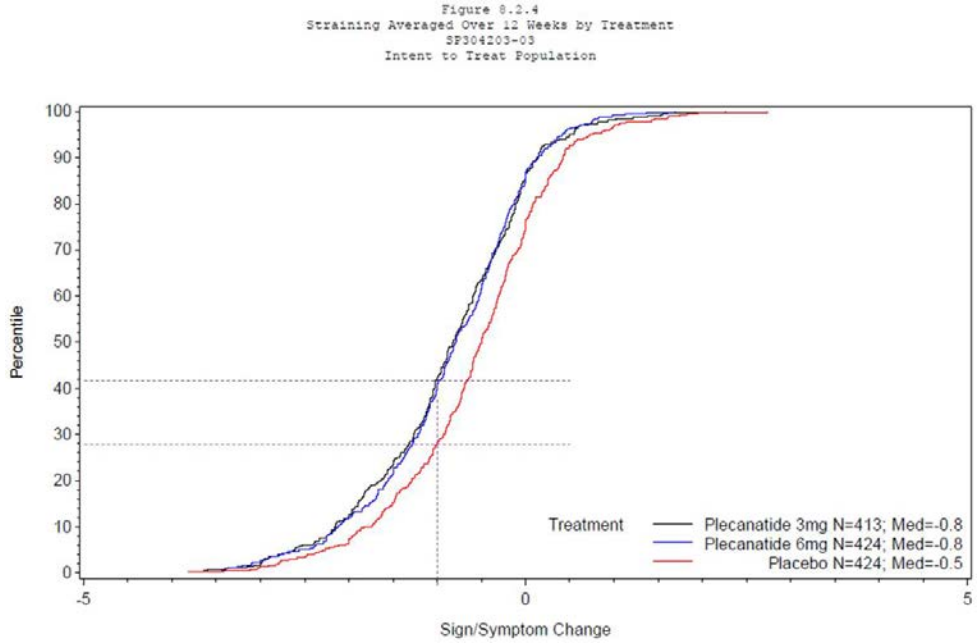
SBM Frequency overall 12 week change by Treatment Group (Study 03)



Stool Consistency overall 12 week change by Treatment Group (Study 03)



Straining overall 12 week change by Treatment Group (Study 03)



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/s/

SARRIT M KOVACS
12/05/2016

ELEKTRA J PAPADOPOULOS
12/05/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208745
Priority or Standard	Standard
Submit Date(s)	1/29/16
Received Date(s)	1/29/16
PDUFA Goal Date	1/29/17
Division/Office	Division of Gastroenterology and Inborn Error Products (DGIEP)
Reviewer Name(s)	Lesley S. Hanes, MD MSc
Review Completion Date	10/6/16
Established Name	Plecanatide
(Proposed) Trade Name	Trulance
Applicant	Synergy Pharmaceuticals, Inc.
Formulation(s)	Tablet
Dosing Regimen	3 mg (b) (4) Oral (PO), once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of Chronic Idiopathic Constipation (CIC)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Adult Patients ≥ 18 years of age

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSBM	complete spontaneous bowel movement
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GC-C	guanylate cyclase-C
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RM	rescue medication
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SGE	special government employee
SOC	standard of care
Study -00	Study SP304203-00
Study -03	Study SP304203-03
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Plecanatide (SP-304) is a synthetic hexadecapeptide analogue of the human endogenous peptide uroguanylin created by Synergy Pharmaceuticals Inc. This drug is an agonist of the GC-C receptor and a new molecular entity. Plecanatide has undetectable bioavailability and acts locally on GC-C receptors within the GI tract.

- Non-proprietary name: plecanatide
- Proprietary name: Trulance
- Pharmacologic class: GC-C receptor agonist
- Dosage form and strength: 3mg immediate-release oral tablet
- Proposed indication: Treatment of CIC in adults
- Proposed dosing regimen: 3mg once daily with or without food

Conclusions on the Substantial Evidence of Effectiveness

This review concludes that this application contains sufficient evidence to support the approval of plecanatide 3mg for the treatment of chronic idiopathic constipation (CIC).

The application included two adequate and well-controlled, phase 3 clinical studies which demonstrated that the primary endpoint of the proportion of patients who were overall complete spontaneous bowel movement (CSBM) responders was significantly greater than placebo for both the plecanatide 3 mg and 6 mg treatment groups ($p < 0.001$). Improvements in CSBM responder rates were seen as early as Week 1 with improvement maintained through Week 12. Additionally, three main secondary endpoint results of weekly CSBMs and spontaneous bowel movements (SBMs) frequency and stool consistency were more clinically meaningful and statistically significant in the plecanatide than the placebo treatment group. Overall, the safety profile of plecanatide treatment appears to be acceptable. Patients in the 3mg plecanatide group had less reports of AEs, particularly gastrointestinal (GI) -related, than patients in the 6mg group.

Although the 6mg plecanatide group experiences efficacy benefit, it did not show a clear efficacy advantage over the 3mg plecanatide group. However, the 6 mg plecanatide dosage may be less

well tolerated due to GI adverse reactions. (b) (4) Hence, although this review discusses both doses of plecanatide, only the 3mg dose is recommended for approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Chronic idiopathic constipation (CIC) represents one of the functional, non-life threatening gastrointestinal (GI) disorders that is described by the ROME criteria. In general, Constipation is a symptom of many diseases and is a collective term used to imply infrequent stools, incomplete bowel movements (BMs), straining, bloating, and hard, lumpy stool. As a prevalent chronic, GI motility disorder, CIC affects an average of 15% of North Americans. Moderate to severe symptoms that are associated with CIC can be debilitating for patients. If left untreated, patients can experience symptoms that are moderate to severe and can have an impact on patient's quality of life. The current treatment armamentarium does not completely meet the needs of the patients with CIC. The available treatments are not effective in all patients and may be accompanied by intolerable adverse events, particularly for the subset of patients who have severe CIC or who are older in age and may be more sensitive to the side effects of treatment for constipation.

Due to the limited number of approved treatments for patients with CIC, additional treatment options are needed for those who do not respond to first-line/ previously used treatment or prescription medications. Plecanatide, as novel endogenous peptide uroguanylin that serves as an agonist of the GC-C receptor, acts locally in the GI tract to provide relief from constipation in patients with CIC.

The plecanatide clinical development program demonstrates the efficacy and safety of plecanatide as a treatment for adults with CIC. The data of two phase 3 adequate and well-controlled studies favored plecanatide (3 mg and 6 mg) over placebo for the primary efficacy endpoint of the proportion of overall complete spontaneous bowel movement (CSBM) responders during the 12-week treatment period. Patients responded to plecanatide after a single week of treatment, and efficacy was maintained throughout the 12-week treatment period. The 3 mg and 6 mg plecanatide treatments were also clinically meaningful and statistically significantly more effective than placebo for the secondary endpoints of weekly CSBM and SBM frequency, stool consistency and straining. Although the treatment difference between each of the plecanatide doses

and the placebo are modest, this drug may offer a new, alternative therapeutic option and may have a clinical impact on some patients who suffer from CIC.

Overall, the analyses of safety show that plecanatide is safe and well tolerated at both the 3 mg and 6 mg doses in the treatment of patients with CIC. The most common AEs were consistent with the known activity of plecanatide. Adverse events were mostly mild or moderate in severity and, apart from those related to the known pharmacology of plecanatide, are thought be probably unrelated to the study drug. Of potential concern, severe diarrhea was more commonly seen in patients receiving the higher 6mg of plecanatide versus the lower dose of 3mg. Additionally, there may be a trend of increased elevated hepatic enzymes, as seen in SAEs, in the 6mg versus 3 mg group.

There exists a theoretical concern regarding potential uroguanylin peptide depletion (UPD) syndrome, caused by immunogenicity to plecanatide which shares structural homology to endogenous uroguanylin. However, in the review of the data presented in the NDA, there are no signals of UPD-related AEs (hypertension, edema, pulmonary edema, hypernatremia, weight gain) with plecanatide at this time.

(b) (4)

Furthermore, pediatric patients have not been studied in the plecanatide developmental program and due to the nonclinical, juvenile toxicology data risks of the occurrence of severe dehydration, plecanatide is contraindicated for patients < 6 years of age. The labeling recommends the avoidance of use in pediatric patients age 6 to less than 18 years of age. This contraindication and avoidance of use will continue until pediatric GC-C ontogeny is further elucidated through an intestinal biopsy study, and safety is demonstrated in older pediatric cohorts. Lactation studies are also needed to determine the safety of plecanatide for breast-fed infants whose mothers are receiving therapy. Finally, adequate anti-drug antibody assays are needed in order to determine the immunogenic potential of plecanatide.

Approval of plecanatide for the use of adult patients with CIC is fully supported by the available evidence of efficacy and safety. Plecanatide is the second drug in a new class of GC-C receptor agonists for the treatment of patients with chronic CIC. It represents an alternative to the treatment armamentarium and an important new therapy to address the significant and growing public health burden of the condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Chronic idiopathic constipation (CIC) represents one of the functional, non-life threatening gastrointestinal (GI) disorders that is described by the ROME criteria. As a prevalent chronic, gastrointestinal (GI) motility disorder, chronic constipation affects from 2% to 27% of North Americans, with an average of 15%. Constipation is a symptom of many diseases and is a collective term used to imply infrequent stools, incomplete bowel movements (BMs), straining, bloating, and hard, lumpy stool. These symptoms have considerable impact on may have concerning impact on the daily life and quality of life of patients who suffer from this condition. While CIC is not a life threatening, condition, its chronic and relapsing nature, including symptoms, such as abdominal pain, infrequent and/ or hard stool production and straining with defecation, may have a significant impact on patients. These chronic symptoms can greatly affect the well-being of patients and potentially patient daily function. CIC may persist without effective treatment and there is a need for additional effective treatment options for patients with CIC.	Although CIC is not a life-threatening condition, it is a prevalent condition. Moderate to severe symptoms that are associated with CIC can be debilitating for patients. If left untreated, patients can experience symptoms that are moderate to severe and can have an impact on patient's quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are currently two approved prescription products on the market indicated for the treatment of CIC. Linaclotide is an oral, once daily guanalyate cyclase-C (GC-C) agonist that acts locally in the gastrointestinal (GI) tract to promote BMs and reduce colonic pain. This medication was approved in 2012 and is indicated for the treatment of both CIC and irritable bowel syndrome with constipations (IBS-C) in adults. The second currently marketed prescription medication is lubiprostone, which was approved in 2006 for the treatment of adults with CIC and is also indicated for the treatment of irritable bowel syndrome with constipation in women 18 and older and in the treatment of opioid-induced constipation in adults with chronic, non-cancer pain. Lubiprostone is a locally acting chloride channel activator that is intended in increase motility in the intestine by increasing intestinal fluid secretion. Current treatment options are not always effective and many patients with severe constipation and CIC do not respond adequately to either first-line treatments or over-the-counter (OTC) laxatives. All available OTC and prescription drugs for CIC are associated with side effects. Moreover, the limited number of available prescription medications for CIC restricts the options for patient treatment. There are many OTC therapies and dietary adjunct used in the management of CIC. First line treatments for constipation currently include the following: increased dietary fiber consumption and supplementation with bulking agents, bowel habit training increased exercise, and increased water consumption. Patients with severe idiopathic chronic constipation often fail to improve fiber supplements or mild laxatives.	The current treatment armamentarium does not completely meet the needs of the patients with CIC. The available treatments are not effective in all patients and may be accompanied by intolerable adverse events, particularly for the subset of patients who have severe CIC or who are older in age and may be more sensitive to the side effects of treatment for constipation. Due to the limited number of approved treatments for patients with CIC, additional treatment options are needed for those who do not respond to first-line/ previously used treatment or prescription medications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Plecanatide 3mg and 6mg given daily for the treatment of CIC over 12 weeks has proven to be effective in increasing the number of , overall CSBM in two phase 3 studies, in comparison to placebo treatment. Based on the evidence in the two phase 3 trials, the effectiveness of plecanatide at the two doses is evident across age, gender and race subpopulations. The effectiveness of the medication in the treatment of CIC occurs sooner than the placebo treatment, in the first week of therapy, and the effectiveness of both doses outweighs the effectiveness evident in the placebo at each of the 12 week trial. In Study -00, the proportion of CSBM responders over Weeks 1 – 12 was significantly greater in patients receiving plecanatide compared to placebo (21.0% in the 3mg group, versus 10.2 %, in the placebo, p<0.001; 19.5% in the 6 mg group, versus placebo, p<0.001). Similarly, in Study -03, the proportion of CSBM responders over Weeks 1 – 12 was significantly greater in patients receiving plecanatide compared to placebo (20.5% in the 3mg group, versus 13.0 %, in the placebo, p<0.003; 20.0% in the 6 mg group, versus placebo, p<0.005) The increases in the stool frequency, via the increase in number of CSBMs and SBMs in a week, may have clinical meaningfulness to many patients who suffer from CIC. Almost twice the number of patients who took plecanatide 3mg and 6mg dosage forms, vs. placebo, were able to fulfill the primary efficacy endpoint of having at least 3 CSBMs per week and an increase of at least 1 CSBM per week above baseline in the same week. In order to be considered a responder, the approximate number needed to treat (NNT) to obtain the effect of the primary endpoint with plecanatide 3mg and 6mg in the Study 1 was 10 and 11 patients, respectively; in the Study 2, and 13 and 14 patients, respectively.	Plecanatide, an agonist of the GC-C receptor, acts locally in the GI tract to provide relief from constipation in patients with CIC. Patients responded to plecanatide after one week of treatment, and efficacy was maintained throughout the 12-week treatment period. Collectively, these results demonstrate the efficacy of plecanatide as a treatment for adults with CIC. Although the treatment difference between each of the plecanatide doses and the placebo are modest, this drug may offer a new, alternative therapeutic option and may have impact on some patients who suffer from CIC. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The 3 mg and 6 mg plecanatide treatments were also statistically significantly more effective than placebo, both over the course of the entire treatment period and for each weekly assessment, for the secondary endpoints of CSBM frequency, SBM frequency, stool consistency and straining. Some variability was observed within subgroups, however, some of these subgroups contained small numbers of patients, which limited the interpretation of data. Since the phase 3 trials were not powered for the statistical analysis of the difference of effectiveness of plecanatide 3mg and 6mg dosages, it cannot be concluded whether one dosage is more effective than the other, however, the efficacy of both doses appeared similar. (b) (4) .	(b) (4)
Risk	The safety profile for both the plecanatide 3 mg and 6 mg doses for the treatment of adult patients with CIC appears acceptable in the analyzed trials. The incidence of AEs was similar in the 3 mg plecanatide, 6 mg plecanatide treatment groups, and placebo (31.7%, 32.5%, and 29.3%, respectively). Adverse events were mostly mild or moderate in severity and, apart from those related to the known pharmacology of plecanatide, judged to be unrelated to the study drug. The most common AEs were consistent with the known activity of plecanatide and included AEs in the system organ classes of gastrointestinal disorders, specifically diarrhea,. The incidence of study-drug-related diarrhea was higher in plecanatide patients than in placebo patients (5.0% versus 1.3%). In addition, 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	Overall, the analyses of safety show that plecanatide is safe and well tolerated at both the 3 mg and 6 mg doses in the treatment of patients with CIC. The observed adverse events were consistent with the known activity of plecanatide and were generally mild in severity. There was a slightly higher rate of certain GI AEs seen in the 6mg dose group, (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	0.3% for 3mg and placebo doses, respectively). Treatment with plecanatide was not associated with any clinically meaningful differences in AE incidence with respect to gender, age, race, or BMI subgroup. Patients who received plecanatide 3mg QD experienced less severe diarrhea and discontinuations due to diarrhea symptoms than the plecanatide 6mg QD group. Overall, the incidences of SAEs and severe AEs were low throughout the plecanatide development program. In the primary safety pool, the incidence of SAEs in the 3mg and 6mg doses were 1.5% and 1.0% in comparison to 1.3% for the placebo. Accordingly, the incidence of severe AEs SAEs in the 3mg and 6mg doses were 2.3% and 2.6% in comparison to 1.5% for the placebo. The SAEs and laboratory analyses showed a potential trend suggestive of an increase in the incidence of elevated hepatic enzymes over time, particularly in the plecanatide 6mg dose group . Plecanatide has not been evaluated in patients younger than 18 years. In nonclinical studies, deaths occurred due to diarrhea-related dehydration within 24 hours in young juvenile mice (1- to 2-week-old mice) following administration of 1 or 2 oral doses of plecanatide. Although no deaths were observed in older juvenile mice (Day 21 or older). There are no studies or available data on plecanatide use in pregnant women to inform any drug-associated risks. Plecanatide is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Additionally, it is not known whether plecanatide is excreted in human milk; however, plecanatide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses.	(b) (4) There is a risk of increased diarrhea and dehydration in young pediatric patients due to increased GC-C receptor density. Data is needed on the ontogeny of the GC-C receptor prior to conducting studies in young pediatric patients. There were no signals UPD-related AEs seen in the clinical development program.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There exists the risk of immunogenicity to plecanatide, a peptide product, and the theoretical risk of uroguanylin peptide depletion (UPD) syndrome, as plecanatide shares structural homology with endogenous uroguanylin. Potential adverse events associated with uroguanylin depletion include hypernatremia, pulmonary edema, peripheral edema, sudden weight gain, and hypertension. No safety signals of UPD were seen in the safety analysis of plecanatide.	
Risk Management	Pediatric patients have not been studied in the plecanatide developmental program and due to the nonclinical, juvenile toxicology data risks of the occurrence of severe dehydration, plecanatide is contraindicated for patients < 6 years of age. The labeling recommends the avoidance of use in pediatric patients age 6 to under 18 years of age. This contraindication and avoidance of use will continued until pediatric GC-C ontogeny is investigated and further elucidated through intestinal biopsies, and older pediatric cohorts are studies. The division is proposing to the Pediatric Research Committee (PeRC) that studies in children <2 years of age are waived. Studies in children 2 to 6 years of age are deferred until the completion of the following: safety and efficacy data are obtained from the older child study from 6 to < 12 years of age; the contraindication statement is modified by supportive data from a FDAAA PMR via the completion a GC-C receptor biopsy study in pediatric patients. Studies in the 6 to < 12 years of age group are deferred until the completion of studies in the 12 to 17 years of age group. Studies in 12 to 17 years of age were deferred until the completion of clinical studies in the adult population.	Labeling indicates that the approval is only for adults. Plecanatide is contraindicated for patients < 6 years of age. The labeling recommends the avoidance of use in pediatric patients age 6 to under 18 years of age. A FDAAA PMR for pediatric biopsy studies are warranted in patients from birth to 6 years of age to assess the ontogeny of the GC-C receptors. In addition, PREA PMRs will occur sequentially beginning with the oldest age cohort. Studies in younger children

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Plecanatide is negligibly absorbed systemically following oral administration and is not expected to result in fetal exposure to the drug. The available data on plecanatide use in pregnant women are not sufficient to inform any drug-associated risk for major birth defects and miscarriage. 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 maximum recommended human dose. The effects of local gastrointestinal and limited systemic exposure to plecanatide are unknown. The developmental and health benefits of breastfeeding should be considered 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. Moreover, in the development adequate immunology assays have not been created to measure for the detection and confirmation of anti-drug-antibodies.	will not be initiated until safety has been demonstrated in older pediatric patients and results from the GC-C biopsy study have been reviewed.

2 Therapeutic Context

Analysis of Condition

Chronic idiopathic constipation (CIC) represents one of the functional, non-life threatening gastrointestinal (GI) disorders that is described by the ROME criteria.[1] While CIC is not a life threatening condition, this condition's chronic and relapsing nature of symptoms, such as abdominal pain, infrequent and/ or hard stool production and straining with defecation, may have a significant impact on patients.[2] As a prevalent chronic, gastrointestinal (GI) motility disorder, chronic constipation affects from 2% to 27% of North Americans, with an average of 15%.[1,3,4] CIC has a higher prevalence in women, those with reduced caloric intake and increasing age. Actual prevalence may be greater than these estimates as not all patients seek medical attention for the condition. These chronic symptoms can greatly affect the well-being of patients and potentially patient daily function. CIC may persist without effective treatment and there is a need for additional effective treatment options for patients with CIC.

CIC is recognized to impact the health-related quality of life (QoL) and studies have shown that the degree of symptom severity correlates negatively with the patient's perceived QoL. In a patient survey about chronic constipation performed by investigator Johanson et al., of 557 patients with CIC, defined by Rome II criteria, 52% stated that their symptoms affected their QoL. Twelve percent (12%) of those patients who worked or went to school experienced reduced productivity and a mean 2.4 days of absence in the month prior to the survey. Most of the participants had used constipation relief therapy and were not completely satisfied due to efficacy and safety concerns.[5] Population studies have shown that in patients with chronic constipation, poor QoL was an important predictor of healthcare utilization and their resultant healthcare costs.

[1] Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. Gastroenterology. 2016 Feb 18
[2] Cash BD, Chang L, Sabesin SM, Vitat P. Update on the management of adults with chronic idiopathic constipation. J Fam Practice. 2007;96:513-519.
[3] Lembo A, Camilleri M. Chronic constipation. N Engl J Med. 2003;349:1360-1368.
[4] Higgins, PD & Johanson, JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004;99:750-759.
[5] Johanson,et al. Chronic constipation: a survey of the patient perspective. Aliment Pharmacol & Ther. 2007. 25, 599-608

The Rome III criteria consensus definition for functional constipation is used for both diagnosis in clinical practice and in current research to define CIC. These criteria are based on both objective and subjective symptoms. The definition states that the diagnosis of CIC should be based upon the presence of the following criteria, for at least three months, in addition to symptom onset at least six months prior to diagnosis:[6]

(1) Must include two or more of the following:
- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- Sensation of incomplete evacuation for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor)
- Fewer than 3 defecations per week

(2) Loose stools are rarely present without the use of laxatives
(3) Insufficient criteria for irritable bowel syndrome (IBS)

While CIC is not a life threatening condition, the chronic and relapsing nature of CIC symptoms such as abdominal pain, infrequent and/ or hard stool production and straining with defecation, may have an impact on patients' lives. These chronic and often painful and bothersome symptoms can greatly affect the well-being of patients and potentially patient daily function. CIC may persist without effective treatment and there is a need for additional effective treatment options for patients with CIC.

2.2. Analysis of Current Treatment Options

Prescription Therapies

There are currently 2 approved prescription products on the market indicated for the treatment of CIC, linaclotide and lubiprostone. Tegaserod was approved for the treatment of CIC but was subsequently withdrawn from the market due to safety concerns.

[6] Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006; 130:1480.

Linaclotide (Linzess®), approved in 2012, is an oral, once daily guanalyate cyclase-C (GC-C) receptor agonist that acts locally in the gastrointestinal (GI) tract to promote BMs and reduce colonic pain. This medication is indicated for the treatment of both CIC and irritable bowel syndrome with constipation (IBS-C) in adults. Linaclotide is a 14-amino-acid synthetic peptide that is structurally related to the ST peptide bacterial enterotoxin and has the same mechanism of action as plecanatide as a GC-C receptor agonist. In studies of patients with CIC, linaclotide increased the percentage of patients who had three or more CSBMs per week, with an increase from baseline of at least one CSBM per week for at least 9 of the 12-week treatment period. This medication also improved BM frequency, stool consistency, and reduced straining.

Diarrhea was the most common adverse reaction in patients treated with linaclotide in both pooled CIC and IBS-C double-blind placebo- controlled trials. Severe diarrhea was reported in 2% of these patients. In these studies, severe diarrhea led to dizziness, syncope or loss of consciousness, electrolyte abnormalities (such as hypokalemia and hyponatremia). Hypotension requiring hospitalization or intravenous fluid resuscitation were reported in patients who were treated with linaclotide. In the label, linaclotide is contraindicated in children less than 6 years of age due the results from juvenile animal studies that have shown that the medication causes severe dehydration in juvenile mice.[7] Other contraindications for linaclotide patients include with suspected mechanical gastrointestinal obstruction.

Lubiprostone (Amitiza®) was approved in 2006 for the treatment of adults with CIC. Amitiza is also indicated for the treatment of IBD-C in adult women and for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain. Amitiza is a locally acting chloride channel activator that is intended in increase motility in the intestine by increasing intestinal fluid secretion. [8] The clinical trials that supported the approval of lubiprostone for CIC utilized an endpoint based on SBMs (not CSBMs). Data from two phase 3 trials demonstrated the therapeutic benefit of lubiprostone in the CIC population. Patients on lubiprostone experienced significant improvement in the frequency of weekly SBMs than those taking placebo within 24 hours after the first dose. Symptom scores were significantly improved with lubiprostone compared to placebo for stool consistency, straining, and constipation severity. The most common adverse events reported in those treated with Amitiza during clinical trials were headache and diarrhea. Additionally, Amitiza is contraindicated in patients with known or

[7] Linzess FPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202811s007lbl.pdf
[8] Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. Dig Dis Sci. 2011 Sep;56(9):2639-45.

suspected mechanical gastrointestinal obstruction.[9]

In addition to these two marketed products indicated for the treatment of CIC, **tegaserod maleate (Zelnorm®)** is a 5-hydroxytryptamine (5HT4) receptor partial agonist which was originally approved in 2002 for women with constipation predominant irritable bowel syndrome (IBS-C) and in 2004 for patients less than 65 years of age with CIC. Diarrhea was the most common adverse event in clinical trials of Zelnorm, including serious AEs of diarrhea associated with hypovolemia, hypotension and syncope. Cases of intestinal ischemia and ischemic colitis occurred during the marketed use of this medication. Furthermore, safety concerns of ischemic cardiovascular events led to the voluntary withdrawal of Zelnorm from the U.S. market in 2007. Zelnorm is currently only available for patients who have failed other therapies through single patient INDs under the FDA's expanded access program.

Over-The-Counter (OTC) Therapies

There are a variety of OTC therapies and dietary adjunct used in the management of CIC. Fiber supplements and bulk forming agents absorb fluid from the intestinal lumen and expand the stool. Bulk forming agents absorb fluid from the intestinal lumen. The resultant increased bulk facilitates peristalsis which increases bowel motility and decreases gastrointestinal transit time. Additionally, stool softeners such as docusate may allow the patient to pass stool without straining although they do not directly result in a bowel movement.

Similar to stool softeners, lubricant laxatives, such as mineral oil, encourage bowel movements by coating the bowel and the stool mass and facilitating the passage of stool. Stimulant laxatives, including bisacodyl, are commonly used for constipation treatment and work by the direct stimulation of the smooth muscle of the colon. Magnesium hydroxide and sorbitol are examples of hyperosmotic laxatives which may be used to draw fluid into the bowel from the surrounding tissue by osmotic activity and provide for softer stools and increased peristalsis. Saline laxatives represent another member of this class of medications and include oral magnesium sulfate preparations.

[9] Amitiza FPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021908s011lbl.pdf

Enemas are widely used to treat constipation. Enemas create a mechanical distention of the bowel that result in evacuation of stool. Moreover, combination products are available OTC that may contain both a stool softener and a stimulant laxative.

Non-medication, behavioral-base therapies include lifestyle modifications, such as increased exercise, increased fluid intake and increased dietary fiber are options for improving the symptoms of constipation. To date, there is insufficient evidence supporting the effectiveness of nondrug interventions, although some studies have shown them to be potentially beneficial.

Conclusion Regarding Current Available Treatments

The current treatment armamentarium does not meet many of the needs of the patients with CIC. The available prescription treatments are not effective in all patients and may be accompanied by intolerable adverse events, particularly for the subset of patients who have severe CIC, or those who are older and may be more sensitive. Patients with severe CIC often fail to respond to OTC therapies such as laxatives, which are typically recommended for discreet episodes of constipation and may not be suitable for chronic use or for the treatment of CIC. Hence, additional therapies are desired by many for the management of CIC. Please see Table 1 below regarding the current treatment armamentarium for CIC.

Table 1: Summary of Approved Therapies for Chronic Idiopathic Constipation (CIC)

Product (s) Name	NDA	Relevant Indication	Mechanism of Action	Year of Approval	Dosing/ Administration	Contraindications and Common AEs
FDA Approved Treatments						
Lubiprostone (Amitiza)	021908	CIC in adults and IBS-C in women	Chloride channel activator	2006	Oral: 24 mcg BID	Contraindication: known or suspected mechanical GI obstruction Common AEs: diarrhea, nausea, headache, abdominal pain, abdominal distention, and flatulence
Linaclotide (Linzess)	202811	CIC and IBS-C in adults	Guanylate cyclase-C agonist	2012	Oral: 145 mcg QD for CIC; on empty stomach	Contraindications: pediatric patients under 6 years of age; patients with known or

					at least 30 minutes prior to fist meal of the day	suspected mechanical GI obstruction Diarrhea, bloating Common AEs: diarrhea, abdominal pain , flatulence, abdominal distention, URI and sinusitis
Zelnorm (tegaserod maleate)[10] **Voluntarily withdrawn**	021200	CIC in adults less than 65 years old and IBS-C in women	Tegaserod is a 5-HT4 receptor partial agonist	2002 for IBS-C 2004 for CIC 2007 withdrawn from the market	Oral: 6 mg BID before meals for 4-6 week courses for IBS-C; continuous therapy for CIC	Contraindications: severe renal impairment, moderate or severe hepatic impairment, history of bowel obstruction, symptomatic gallbladder disease, suspected Sphincter of Oddi dysfunction, or abdominal adhesions Common AEs: Diarrhea associated with hypovolemia, hypotension and syncope, abdominal pain, nausea, abdominal distension, URI, sinusitis Rare: intestinal ischemia, ischemic colitis Withdrawn from the market in 2007 due to an imbalance in cardiovascular ischemic events identified in a meta-analysis from 29 placebo controlled trials.

Source: Reviewer's Table adapted from Wald, Arnold. Up-to-date review: Etiology and evaluation of chronic constipation in adults. Dec. 2014

[10] Zelnorm was voluntarily withdrawn from the market due to safety concerns and is now available only through expanded access INDs.

Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Plecanatide (SP-304) is a new molecular entity (NME) that is not approved or marketed in the United States. It is an immediate-release solid formulation tablet that is intended for chronic oral administration for the treatment of CIC in adults. The development of plecanatide for the treatment of CIC was conducted under IND 074883. Plecanatide is also being developed for the treatment of IBS-C (b) (4).

3.2. Summary of Pre-Submission/Submission Regulatory Activity

IND 74883 was opened in the United States on May 3, 2008 for the product SP340 (guanilib, plecanatide) in the treatment of CIC. (b) (4) This summary will focus on regulatory activities related to the CIC treatment indication. Pre-submission regulatory activities related to this submission included formal face-to-face end of phase 2 (EOP2) and Pre NDA meetings between the FDA and the sponsor. In additional, there were multiple written correspondences during the development program. The primary efficacy endpoint, dose selection for the Phase 3 trials, the iPSP, and anti-drug- antibody (ADA) assays were developed, or in the process of development, in communication with the FDA. NDA 208745 was submitted on January 29, 2016 as a 505(b)(1) application. NDA 208745 has a standard review designation with a PDUFA goal date of January 29, 2017.

Table 2 below summarizes pre-submission regulatory meetings and correspondence and is followed by additional detailed information on key meetings and correspondence.

Table 2: Pre-Submission Regulatory History for NDA 208745

Date	Regulatory Action(s)
3 October 2006	Pre-IND 74883 meeting (b) (4) (b) (4) The agency required the study of the clinical trial formulation of SP-304 in nonclinical studies prior to initiating the Phase 1 clinical trial (additional details below).
29 May 2008	IND 74883 acknowledgement letter for submission for SP-304 (guanlib), (b) (4), by Synergy Pharmaceuticals, Inc.
20 February 2009	Non-clinical advice regarding Monkey GLP study dose and CMC discussion. The MTD for a planned nonclinical toxicity study guidance provided.
4 March 2009	The Agency sent a Partial Clinical Hold letter for IND 74883 due to insufficient information to assess risk to human subjects based on nonclinical data.
5 February 2010	Letter from the Agency Partial Clinical Hold removed for IND 74883.
6 December 2010	Type C meeting for CIC which discussed the primary endpoint, handling of missing data and the secondary endpoints. Agreements were made between the FDA and the sponsor regarding these topics.
25 July 2012	Type C preliminary responses to the sponsor regarding waiving carcinogenicity studies were sent. The agency did not agree to this waiver and referred the sponsor to the ICH guidances S1C (R2) and S1B, and the FDA guidances "Carcinogenicity Study Protocol Submissions" and "Special Protocol Assessment" for details. Face-to-face meeting schedule for July 23, 2012 was canceled since the preliminary responses were sufficient.
31 January 2013	Non-clinical, Executive CAC carcinogenicity SAP response (Mouse) dated January 31, 2013. The response discusses mouse carcinogenicity study protocol and dose selection.
12 April 2013	Non-clinical, Executive CAC carcinogenicity SAP response (Rat) dated April 12, 2013. The response discusses rat carcinogenicity study protocol and dose selection.
5 June 2013	Type C EOP2 CMC meeting discussed the CMC development program. Refer to the meeting minutes dated June 5, 2013 for further details.
31 July 2013	Type B EOP2 meeting regarding Clinical and Nonclinical issues. Meeting was cancelled since the preliminary responses were sufficient. (Please see additional details below). Written responses are dated July 31, 2013.
7 August 2014	Thorough QT Study Waver requested. The Agency subsequently agreed to the this waiver

	request.
18 June 2014	The Agency's Advice letter regarding Juvenile Toxicity CMC draft protocol dated May 6 2014.
28 October 2014	Type C EOP2 CMC meeting discussed the CMC development program. Refer to the meeting minutes dated October 28, 2014 for further details.
18 November 2014	The Agency's response letter to SPA Mouse Carcinogenicity. The Agency did not concur with the sponsor's original and provided additional recommendations.
22 January 2015	The Agency's response letter to Rat carcinogenicity with additional recommendations.
6 February 2015	The Agency sent iPSP Agreement letter for IND 74883, submitted on December 29, 2014.
16 March 2015	The Agency sent an Advice Letter Upon Pediatric Study Plan in response to Pediatric Study Waiver request for the treatment of CIC in the birth to (b) (4) age group.
28 July 2015	Type C CMC meeting discusses the CMC development program. Refer to the meeting minutes dated August 11, 2015 for further details.
5 August 2015	Type B Pre-NDA meeting (Please see additional details below). Meeting minutes dated September 21 2015.
18 January 2016	Letter from the sponsor regarding the delay in the immunogenicity screening assay and patient data.
19 January 2016	The sponsor was granted a small business waiver for the fiscal year 2016 human drug application free for NDA 208475 for plecanatide (SP-304).

Source: Reviewer's Table

Key Meetings and Correspondences

1. October 3, 2006: Pre-IND meeting

(b) (4)

(b) (4)

Because the formulation to be used in the clinical trials was different from that used in the nonclinical studies, the FDA require that the sponsor study the clinical trial formulation in nonclinical studies prior to initiating the Phase 1 clinical trial.

2. December 6, 2010: Type C meeting

a) **Primary endpoint:** From the meeting minutes, the FDA indicated the following regarding the primary endpoint: a weekly responder should be defined as a patient who has ≥3 Complete Spontaneous Bowel Movements (CSBMs)/ week and an increase from baseline of ≥1 CSBM/week for that week. The FDA further indicated that the definition for a monthly responder should require, at a minimum, that the patient be a weekly responder for at least 75% of the weeks, e.g. at least three out of four weeks, in that month. Additionally, patients should be considered to be an overall responder if he or she is a monthly responder for two out of the three months during the treatment period (including the last month of the treatment period).

b) **Clinically meaningful change in CSBM:** The FDA stated that an increase from baseline of ≥ 1 CSBM/ week in patients with CIC may be considered clinically meaningful when coupled with an improvement of constipation (demonstrated as ≥3 CSBMs/ week).

c) **Handling of Missing Data:** The FDA recommended that a conservative approach should be taken and that a method to compute a weekly CSBM frequency rate was needed, in the context of missing data. An example of how to handle missing data was provided: In a given week, the number of CSBMs/ week could be calculated as follows:

(Number of CSBMs during that week ÷ Number of days with non-missing CSBM assessments during that week) x7.

Additionally it was discussed that subjects with fewer than 4 days of CSBM assessments during the week, the number of CSBMs should be set to missing for that week. As a result, in the computation of the primary endpoint, any patient with fewer than 4 days of CSBM assessments made during a given week should be categorized as a "non-responder" for that week.

d) Constipation-associated secondary endpoints were also discussed. The Agency recommended

that the sponsor evaluate the symptom reports by disease severity to ensure that the symptoms that are selected for the daily symptom diary adequately reflect the entire spectrum of disease severity in the intended target population, as well as the diversity of the target population with chronic constipation.

3) July 31, 2013: End of Phase 2 (EOP2) meeting

Preliminary responses were provided for an EOP 2 meeting originally scheduled for July 31, 2013. Preliminary written responses were felt to be sufficient, and the sponsor subsequently cancelled the face-to-face meeting. Key agreements that were conveyed in writing included:

a) **Dose selection:** The sponsor proposed evaluating a higher plecanatide dose, 6mg QD, in their phase 3 program, in addition to 3 mg QD dose. The FDA agreed that the 6mg plecanatide QD dose did not show safety concerns and could be evaluated in the phase 3 trials to potentially support approval of this higher dose.

b) **Primary efficacy endpoints**: The primary efficacy endpoint in the proposed study, SP304203-00 planned to be the proportion of patients who are complete spontaneous bowel movement (CSBM) overall responders for the 12-week treatment period. A CSBM weekly responder was defined as a patient who has ≥ 3 CSBMs per week and an increase from baseline of ≥ 1 CSBM for that week. An overall responder is a patient who is a weekly responder for at least 9 of the 12 treatment weeks, including at least 3 of the last 4 weeks. The FDA agreed with the proposed primary endpoint for an indication of CIC which was proposed .

C) Secondary efficacy endpoints: Secondary endpoints selected for Study SP304203-00 were similar to those evaluated in the previous CIC study (SP304202-10) including changes over the 12-week treatment period in the frequency of CSBMs and SBMs, change in stool consistency as measured by mean change in BSFS, reduction in straining, time to first SBM and CSBM, percentage of patients achieving a mean increase in CSBMs of 1 or more over 12 weeks, global assessments of constipation severity, change in constipation and treatment satisfaction, patient assessment of constipation symptoms (PAC-SYM), and quality of life (PAC-QOL).

As discussed in the PIND meeting, the agency stated that most of the secondary endpoints would be considered exploratory in nature and unlikely to support labeling claims. Specifically, the FDA stated that with the exception of stool consistency based on the BSFS, we consider the

proposed secondary endpoints to be exploratory in nature and unlikely to support label claims. In addition, the Daily Symptom Diary does not appear to be a validated instrument for proposes of supporting symptomatic claims.

c) **Thorough QTc (TQT) Study:** The sponsor contended that TQT study was not needed for the NDA assuming limited systemic exposure of plecanatide was presented. Subsequently, the FDA agreed that a study was not warranted based on submitted evidence in a letter dated September 7, 2014.

4) February 6, 2015: Pediatric iPSP Agreement

a) Request for waiver for plecanatide for the treatment of CIC in the birth to (b) (4) age group was requested. Insufficient data exist to support an unmet need for the treatment of constipation in this age group. Constipation, and its associated symptoms, can be related to infant formula feeding in this age group and often resolves with changes in formula feeding pattern or specific content of infant formula. Furthermore, considerations related to the need for caregiver questionnaires to assess signs and symptoms of CIC make it impractical to perform clinical studies of CIC in this age group. Consequently, a waiver was sought for the study of the CIC indication in the birth to (b) (4) age group, due to studies being impracticable in this pediatric population.[11]

b) Deferrals for pediatric plecanatide trials were requested (b) (4) (b) (4) The deferrals are based on the conduction and the data results from ongoing juvenile nonclinical studies and C-GMP receptor studies in the intestine biopsies of children during routing clinical care.

5) August 5, 2015: Type B Pre-NDA Meeting

This was a face-to face meeting. Key agreements and discussion points included:

a) The FDA agreed that the sponsor does not need to evaluate whether plecanatide is a substrate for cytochrome P450 enzymes that are present in the GI tract.

[11] See section 8.8.3 regarding the change in waiver, requested partial deferral and study cohort age ranges.

b) Per the ICH E1 guidance, for the evaluation of the safety of the chronic use of plecanatide, the FDA recommended that the sponsor should provide data regarding at least 100 patients exposed to plecanatide, for a minimum of 1 year. After the meeting, the sponsor submitted additional information including numbers of patients who had 12 months of consecutive exposure to plecanatide at each the 3mg and 6mg doses (i.e., excluding those patients who completed phase 2 clinical studies and had a break in therapy before the long term safety study that resulted in <6 months of exposure at any time). The exposure numbers of patients were reported to be 159 at the 3 mg dose and 325 at the 6 mg dose. These numbers were acceptable to the Division.

c) The Agency and sponsor discussed the sponsor's approach to evaluate the immunogenicity potential of plecanatide. The agency recommended that the sponsor submit the screening assay validation information when it becomes available and expressed concerns that there is no confirmatory assay to eliminate false positive samples. This may confound the ability to establish relationships between ADA and safety and efficacy.

(b) (4)

e) The Agency agreed that there was no requirement to include risk evaluation and mitigation strategies or elements with the NDA submission.

f) The Agency agreed that the proposed pooling strategy for the ISS and ISE appeared appropriate.

g) The Agency agreed that plecanatide could be taken without regard to food assuming that the phase 3 formulation was the same as the to-be-marketed formulation.

5) January 18, 2016: Response to an Information Request (IR)

The Applicant submitted a letter to the Agency stating that the immunogenicity screening data of patient serum samples for anti-plecanatide antibodies in Phase 3 studies SP304203-00, SP304203-03 and long-term safety study SP304203-01 will not be available in time for the initial

NDA submission due to technical issues in the development of assays. The sponsor indicated that they planned to provide all immunogenicity assays and data by 120 days of the NDA submission. This was discussed at multiple pre-NDA meetings, including the August 5, 2015 meeting.

3.3. Foreign Regulatory Actions and Marketing History

Plecanatide is not marketed in any foreign markets at the time of this review

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDA OSI inspections and evaluation were reported during this review process. Site investigations were performed at six (6) clinical sites. In addition, a contract research organization (CRO) and the sponsor were inspected for this application. Two (2) CI sites have the final classification of voluntary action indicated (VAI), and the violations cited are not considered to have an impact on data integrity. The four (4) clinical site inspections have classifications of no action indicated (NAI). Both the sponsor and CRO sites have the classifications of NAI.

Per OSI: During the process of selecting clinical sites for inspection, it was noted that two CI sites that participated in study SP304203-03 were classified as Official Action Indicated (OAI) for previous inspections conducted as a result of complaints. The first site's investigator, Farid Marquez of site #402, which enrolled 16 patients. This investigator was disqualified from clinical investigations on August 6, 2015.[12] The second site investigator, Cheta Nand of site #362, enrolled 14 patients and an OAI letter was issued March 10, 2016.[13] It was communicated to the review division during the mid-cycle meeting that the data from these sites be considered

[12] http://www.accessdata.fda.gov/scripts/SDA/sdDetailNavigation.cfm?sd=clinicalinvestigatorsdisqualificationproceedings&id=

[13] http://www fda.gov/iceci/enforcementactions/warningletters/2016/ucm493102 htm.

unreliable and be removed from analyses and the ultimate label. Based on the violation history of these investigators, sites #362 and #402 were removed from the major efficacy and safety review analysis. The inspected sites and final classification are summarized in the Table 3 below:

Table 3: OSI Inspection of Sites, CRO, and Sponsor Synergy Pharmaceuticals Inc.

Name and type of inspected entity/Address	Protocol # /Site # # of Subjects	Inspection Date	Classification
CI: Elena Valor, M.D. 9240 Sunset Drive, Suite 116 Miami, FL 33173	SP304203-00/ Site 149/ 41 Subjects	April 26 to 28, 2016	VAI
CI: William Koltun, M.D. 9040 Friars Road, Suite 540 San Diego, CA 92108	SP304203-00/ Site 224/ 35 Subjects	May 25 to June 2, 2016	VAI
CI: John Lentz, M.D. 2121 Fountain Drive, Suite A. Snellville, GA 30078	SP304203-03/ Site 291/ 38 Subjects	April 11 to 25, 2016	NAI
CI: Felix Penate, M.D. 8260 West Flagler Street, Suite 2N Miami, FL 33144	SP304203-03/ Site 415/ 43 Subjects	April 25 to 29, 2016	NAI
CI: Sady Alpizar, M.D. 3434 W. Columbus Drive, Suite 106 Tampa, FL 33607	SP304203-03/ Site 495/ 33 Subjects	May 9 to 13, 2016	NAI
CI: Rosa Suarez, M.D. 434 SW 12th Ave., Suite 302 Miami, FL 33130	SP304203-00/ Site 631/ 26 Subjects	May 31 to June 10, 2016	NAI
CRO: (b) (4)	SP304203-00 SP304203-03	July 6 to 7, 2016	NAI
Sponsor: Synergy Pharmaceuticals Inc. 420 Lexington Ave, Suite 2012 New York, New York 10170	SP304203-00 SP304203-03	August 1 to 4, 2016	NAI

Source: From OSI Susan Leibenhaut, MD; Compliance Classifications; NAI = No deviation from regulations. VAI = Deviation(s) from regulations. OAI = Significant deviations from regulations. Data may be unreliable. Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Overview of Inspection Findings

1. Clinical Site 149 (Study -00)
Form FDA 483 was issued at this site for allowing 9 ineligible patients to remain in the study once deviations were know, out of 21 reviewed records. Additionally, assessments of 7 patients did not have post dose ECGs and lacked patient assessment questionnaires. The clinical investigator responded to the FDA and re-educated the staff on the institutional procedures. The violations noted were documented in the CSR and did not have a significant impact on patient safety or data integrity. Although this site was issued at VAI, the results from this site's data may be used to support the indication.

2. Clinical Site 224 (Study -00)
Form FDA 483 was issued at this site for inadequate drug accountability records. Particularly, the quantity of tablets per kit returned to the sponsor was not recorded by the site. The investigatory at the site proposed adequate corrective action in his response. Although this site was issued at VAI, the results from this site's data may be used to support the indication.

3. Clinical Site 291 (Study-03)
Form FDA 483 was issued at this site for failure to conduct the investigation in accordance with the investigational plan. In particular, issues that were addressed included the late occurrence of post-dose EKGs (although within allotted time window) and adequate pill accounting and transcription errors. The studies appeared to have been conducted adequately and the results from this site's data may be used to support the indication. The investigatory at the site proposed adequate corrective action in his response. A NAI classification was provided and the results from this site's data may be used to support the indication.

4. Clinical Site 415 (Study-03)
No significant regulatory violations were noted that required the issuance of a Form FDA 483. The studies appeared to have been conducted adequately and the results from this site's data may be used to support the indication.

5. Clinical Site 495 (Study-03)
No significant regulatory violations were noted that required the issuance of a Form FDA 483. The studies appeared to have been conducted adequately and the results from this site's data may be used to support the indication.

6. Clinical Site 631 (Study-00)
No significant regulatory violations were noted that required the issuance of a Form FDA 483. The studies appeared to have been conducted adequately and the results from this site's data may be used to support the indication.

7. CRO: (b) (4)
No violations were noted and no Form FDA 483 was issued. There were defects found in 2014 in eligibility reports due to daylight savings time. The company addressed this issue and corrected the programming errors.

8. Synergy Pharmaceuticals, Inc.
Review of the sponsors documents did not note any significant deficiencies in the general conduction of the protocols, and oversight of contract research organizations, and handling of data. Additional, the Form 1572s, financial disclosure, and quality assurance

Please see OSI Susan Leibenhaut, MD review for further information.

Reviewer comment: OSI reports are complete. Four of the six sites were classified as NAI. Two sites, #149 and #224 of Study -00 were classified as VAI, for the reasons summarized above although these violations would not be expected to adversely affect data integrity. At site #149, nine out of 21 patients had noted violations that included allowing ineligible patients to remain in the study. Site 224 did not properly inform the sponsor about the number of tablets returned to the site. These issues most likely did not have an impact on the study results. Form FDA 483 were issued at these sites and OSI received adequate responses from the investigators who made appropriate adjustments. OSI recommended that the data from all sites, including the two sites classified as VAI, could be used in this application. This reviewer agrees with the OSI assessment.

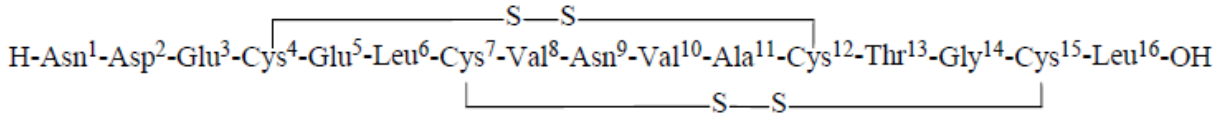
4.2. Product Quality

Plecanatide is a synthetic hexadecapeptide that is an analog of uroguanylin, a naturally occurring natriuretic peptide. The drug product is an immediate release solid oral dosage form tablet comprised of plecanatide, microcrystalline cellulose, and magnesium stearate. The drug product formulation that is planned for marketing is the same formulation used in the phase 3, study -00 and -03 trials. Plecanatide drug substance is manufactured by (b) (4)

(b) (4) and the drug product is manufactured by (b) (4) and packaged by (b) (4) for Synergy. The tablets are white to off-white, plain, round tablets de-bossed with "SP" on one side and "3" on the other side.

Plecanatide shares the same amino acid sequence as uroguanylin with the exception of a single amino acid residue, a glutamic acid rather than aspartic acid at position 3. Plecanatide contains 4 cysteine residues that form 2 intramolecular disulfide bonds, important for generating the peptide conformation necessary for binding to the GC-C receptor. The primary amino acid sequence of plecanatide is shown below in Figure 1.

Figure 1: Plecanatide Amino Acid Sequence



Source: Sponsor's Submission, Clinical Overview

Chemical Formula: C64H104N18O26S4
Molecular weight: 1682.88

See the OPQ review by Zhengfang Ge, PhD, for additional details.

4.3. Clinical Microbiology

Plecanatide is not an antimicrobial or antiviral drug. There is no clinical microbiology data for this compound.

4.4. Nonclinical Pharmacology/Toxicology

In summary, plecanatide administration did not cause any overt effects on key cardiovascular, central nervous system, or respiratory systems at doses in excess of the maximum recommended human dose (MRHD) of 6 mg/day.

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

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

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

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

4.5.2. Pharmacodynamics

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

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

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

4.5.3. Pharmacokinetics

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

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

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

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

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

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

Table 4 contains a summary of the plecanatide phase 2 and 3 trials for CIC treatment submitted with this NDA.

Table 4: Overview of Clinical Development Program Supporting Efficacy and Safety of Plecanatide for CIC

Trial Identity	Trial Design	Dosing Regimen/Placebo Schedule/ Route	Primary Endpoint	Treatment Duration/ Follow Up	Study Enrollment (Safety population) and Treatment Arms	Number of Randomized Patients/ Number in ITT Efficacy population* and Treatment Arms	Study Population	Number of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
SP304203-00	Phase 3, 12-week, multicenter, randomized, DB, placebo-controlled, efficacy and safety study of	3 mg and 6 mg plecanatide oral tablets or placebo, QD, administered without respect to food intake	Proportion of patients who were durable overall complete spontaneous bowel movement (CSBM) responders over the 12-week treatment period. SBM= BM occurring in the absence of laxative use within 24 hours of the BM	2 week pre-treatment period, 12-week treatment period, 2-week follow-up	N= 1389 474 at 3 mg, 457 at 6 mg, 458 Placebo	N=1394/1346 453 at 3 mg, 441 at 6 mg, 452 Placebo	Eligible patients were males and females aged 18 to 80 years, inclusive, who met	183 centers in the U.S. and Canada (164 sites randomizing patients)

SP304203-03	plecanatide oral (tablets) in adult patients with CIC		CSBM= a SBM with the sense of complete evacuation CSBMs weekly responders were patients who had: ≥3 CSBMs per week; and an increase from baseline of ≥1 CSBM for that week Overall CSBM responders were weekly responders at least 9 of the 12 treatment weeks overall CSBM responders were CSBM weekly responders at least 3 of the final 4 weeks		N= 1402 467 at 3 mg, 469 at 6 mg, 466 Placebo	N= 1410/1337 443 at 3 mg, 449 at 6 mg, 445 Placebo	modified Rome III criteria for CIC disease criteria based on history and met the two-week pre-treatment EHD (electronic handheld device) symptom and compliance criteria	180 centers in the U.S. (162 sites randomizing patients)

SP304-20210	Phase 2b, randomized, DB, PBO-ctrl, repeat-dose, dose-ranging study evaluating safety and efficacy of plecanatide in adults with CIC	0.3, 1.0, and 3.0 mg QD, orally plecanatide capsule			N= 948 712 plecanatide (567 for 12 wk) 236 PBO	N= 951/946 (mITT) 237 at 0.3 mg, 238 at 1 mg, 237 at 3 mg, 234 Placebo	Eligible patients were males and females aged 18 to 75 years, inclusive, who met modified Rome III criteria for CIC	121 centers in the U.S. (113 sites randomizing patients)
Studies to Support Safety								
Trial Identity	**Trial Design**	**Plecanatide Regimen/ schedule/ route**	**Primary Endpoint**	**Treatment Duration/ Follow Up**	**Study Enrollment (Safety population) and Treatment Arms**	**Number of Randomized Patients/ Number in ITT* (Efficacy population) and Treatment Arms**	**Study Population**	**No. of Centers and Countries**
SP304203-01	Phase 3, Open-label, long-term safety study	3 or 6 mg, QD, plecanatide tablets, orally		Up to 2 years of dosing 72-weeks	N= 1782 230 at 3 mg 1552 at 6 mg; 446 for >52 wk	n/a	Adults with CIC	

Other Studies Pertinent to the Review of Efficacy and Safety								
SP304201-09	A phase 2a multiple-dose, 14-day treatment study was conducted at doses of plecanatide versus placebo to evaluate safety, PK, and PD effects of plecanatide	4 plecanatide dose cohorts 0.3, 1, 3, and 9 mg Plecanatide capsules Once daily orally (fasted)	safety, PK, & PD effects of plecanatide Monitoring of AEs, clinical labs, vital signs, ECGs, physical exams	14 days of dosing Follow-up 7 days after last dose	N = 78 14 at 0.3 14 at 1 mg, 15 at 3 & 9 mg 20 Placebo	n/a	Adults with CIC	16 centers in the U.S. (14 sites randomizing patients)
(b) (4)								

Source: Reviewer's Table Summarized from Sponsor's Integrated Summary of Efficacy and Integrated Summary of Safety Source: Reviewer's Table Summarized from Sponsor's Integrated Summary of Efficacy and Integrated Summary of Safety; * Note: ITT populations for Studies SP304203-00 and SP304203-03 include subjects not dosed and exclude duplicate non-index patients.

5.2 Review Strategy

For this NDA submission, the phase 3, DB, PC studies SP304203-00 and SP304203-03 were reviewed in detail for safety and efficacy. These two studies were identical in design, except for the PK substudy included in the SP304203-03 trial. The primary and secondary objectives, entry criteria, treatment, study visits and procedures, control procedures, endpoints, and statistical plans were identical. Protocol items that differ between the two studies are highlighted in Section 6 below.

Details of the study design and conduct, and analyses of the results, of these two trials are contained in Section 6: Review of Relevant Individual Trials Used to Support Efficacy. As previously stated, the trial designs were identical in design, thus the protocols and results from the studies are described together in Section 6.1.1. Efficacy results are presented as side by side tables. The integrated study results are discussed in Section 7: Integrated Review of Effectiveness, and an integrated safety review is provided in Section 8: Review of Safety.

For the general approach to the assessment of the evidence in the application, the sponsor's analyses and this reviewer's analysis and commentary is presented. This reviewer worked closely with the statistical reviewer to verify efficacy analyses performed by the applicant. Key safety analyses were performed by this reviewer. Confirmation of demographic and disposition tables, and well as safety analyses, were conducted using JMP and JReview statistical programs. JumpStart service was provided by the Computational Science Center (CSC) at the Center for Drug Evaluation and Research (CDER) to assess data fitness and provide exploratory safety analyses for these 2 studies.

Trial SP304-20210, the phase 2b repeat-dose, dose-ranging study, is considered supportive and data is primarily used in the review of overall plecanatide program safety and analysis of information relevant to dosing recommendations. This study was reviewed in Section 6 and Section 8. This study was not included in the sponsor's integrated analysis of efficacy, as a capsule formulation of plecanatide, different from the tablet that is intended for approval, was used in this trial.

All of the trials listed in the table above are discussed in the Section 8 safety review. This section will also include relevant safety data from the phase 1 studies SP304101-08 and SP304101-09 (see appendix) that involved healthy adults. The safety data at the time of the

NDA submission from the open-label extension study SP304203-01 and data from the 120-day update are also presented in section 8. (b) (4)

(b) (4)

6 Review of Relevant Individual Trials Used to Support Efficacy

Studies SP304203-00 and SP304203-03

As both studies were identical in design, with the exception of the PK substudy in SP304203 -03, the trial designs for both studies are described together below, with any differences noted.

6.1.1. Study Design

Title

SP304203-00: A Randomized, 12-Week, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Plecanatide (3 mg and 6 mg) in Patients with Chronic Idiopathic Constipation (CIC)

SP304203-03: A National, Randomized, 12-Week, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Plecanatide (3mg and 6mg) in Patient with Chronic Idiopathic Constipation (CIC)

Study Overview

SP304203-00
Study SP304203-00 was a multicenter, double-blind, parallel group, placebo-controlled study designed to assess the safety and efficacy of plecanatide (3 and 6 mg) a total of 1394 adult patients with CIC were randomized at 164 clinical sites in the US (153 sites) and Canada (11 sites). This study included a 12-week double blind treatment period with efficacy assessments at 4, 8, and 12 weeks and continuation to week 14 for post-treatment efficacy and safety data. The first patient was pre-screened on December 3, 2013 and the last patient completed his/ her last visit on April 23, 2015.

SP304203-03
Similarly, study SP304203-03 was a multicenter, double-blind, parallel group, placebo-controlled study designed to assess the safety and efficacy of plecanatide (3 mg and 6 mg). A

total of 1410 adult patients with CIC were randomized at 162 clinical sites in the US. This study included a 12-week double blind treatment period with efficacy assessments at 4, 8, and 12 weeks and continuation to week 14 for post-treatment efficacy and safety data. Nine sites enrolled 95 patients in a pharmacokinetics (PK) sub-study with intense PK sampling. The first patient was prescreened on May 16, 2014 and the last patient completed his/ her last visit on May 13, 2015.

Primary Objective

SP304203-00 and -03
The primary objective of these trials was to evaluate the safety and efficacy of plecanatide of 3 mg and 6 mg once daily (QD) doses as compared to placebo , in patients with CIC.

Secondary Objectives

SP304203-00 and -03
To evaluate the effect of 3 mg and 6 mg plecanatide on secondary efficacy endpoints included the frequency of spontaneous (SBM) and complete spontaneous bowel movements, which (CSBMs), stool consistency, straining, treatment satisfaction, and abdominal symptoms associated with constipation.

Study Design

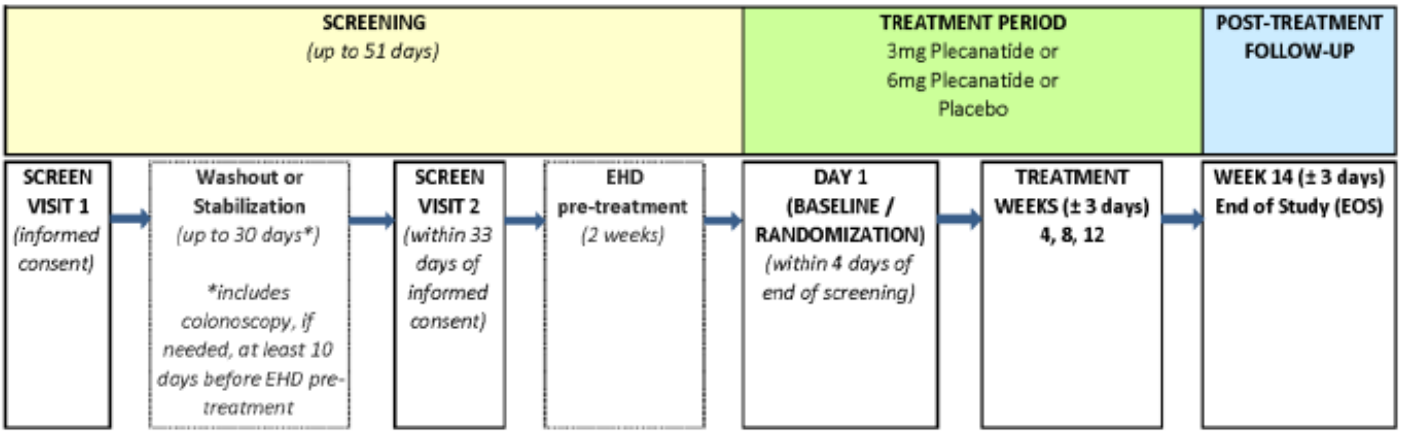
SP304203-00 and -03
Both studies were phase 3, randomized, 12-week, multicenter, double-blind, parallel group, placebo-controlled trials in patients with chronic idiopathic constipation (CIC). The trials consisted of a Pre-Treatment phase which included an initial screening visit. If needed a colonoscopy screening for colon cancer was performed and/or a washout of prohibited medications or stabilization of diet or medical condition occurred following the initial screening. In such cases, a second screening visit to determine eligibility following this washout or stabilization period. Eligible patients were provided an electronic hand-held device (EHD) to complete daily diary entries as part of a 2-week Pre-Treatment screening assessment. This 2-

week period was intended to confirm eligibility and compliance with the daily diary, as well as establish baseline values for efficacy analyses.

Patients determined to be eligible following the 2-week Pre-Treatment screening assessment were to be randomized in a 1:1:1 fashion to plecanatide 3 mg, plecanatide 6 mg, or placebo and were entered into the 12 week Treatment Period. At the end of the 12 weeks, patients were to return to the clinical site for an End of Treatment safety and efficacy assessment. This was followed by a 2-week Post-Treatment Period and a final End of Study efficacy and safety assessment.

The total planned duration of the trial was approximately 16 weeks from the signing of informed consent through the post-treatment period. This period could be extended to ~20 weeks for patients requiring washout of a prohibited concomitant medication or stabilization of a medical condition existing before the pre-treatment period. See the Figure 2 below for the Study Design.

Figure 2: Studies SP304203-00 and -03 Clinical Study Design



Source: Sponsor's Protocols for Studies SP304203-00 and SP304203-03

Key Inclusion Criteria

SP304203-00 and -03

Patients were entered into the study only if they met all of the following inclusion criteria:

1. Patient was willing and able to participate in the study for the required duration, could understand and was willing to sign the informed consent form (ICF), and agreed to undergo all protocol-related tests and procedures.
2. Patient was able to complete all required Daily BM and Symptom electronic diary entries during the 2-week Pre-Treatment Assessment Period and for the duration of the study (i.e., the 12-week Treatment Period and the 2-week Post-Treatment Period). Patient agreed to receive a reminder daily via their electronic hand-held device (EHD) if they did not complete their daily electronic diary entries.
3. Males or females were between 18 and 80 years of age (inclusive); females were not pregnant or lactating.
4. Patient had a body mass index (BMI) between 18 kg/m2 and 40 kg/m2 (inclusive) provided the patient did not have medical complications associated with morbid obesity.
5. Female patients of non-childbearing potential who were surgically sterile or postmenopausal. To be considered post-menopausal, female patients had to be without menstruation for 12 consecutive months before Screening and had an elevated follicle stimulating hormone (FSH) consistent with menopause.
6. Females who were still menstruating had to be able to differentiate the abdominal symptoms associated with CIC from those associated with their menses (otherwise protocol assessments of these symptoms could be confounded).
7. Male and female patients of childbearing potential agreed to use one of the following methods of birth control from the time of signing the ICF to 2 weeks after receiving the last dose of study drug. Note that abstinence was not considered an acceptable form of contraception for the purposes of this study.
    - Hormonal contraceptive (e.g., oral contraceptive, implanted or injected hormonal contraceptive) at least 2 months prior to enrollment
    - Use of double-barrier contraception (e.g., condom with spermicidal foam/gel/film/cream/suppository)
    - Intrauterine device (IUD)

- Surgical sterilization (males who had a vasectomy or females with bilateral oophorectomy, hysterectomy, or tubal ligation)
- Maintain a monogamous relationship with someone who was surgically sterile or was not of childbearing potential (e.g., postmenopausal)

8. Patient met the modified Rome III functional constipation diagnostic criteria, for the last 3 months with symptom onset at least 6 months prior to diagnosis:
    - Patient reports that loose stool is rarely present without the use of laxatives
    - Patient does not meet Rome III criteria for Irritable Bowel Syndrome with Constipation (IBS-C)
    - Patient reports < 3 defecations per week
    - Patient does not use manual maneuvers (e.g. digital evacuation, support of the pelvic floor) to facilitate defecations
    - Patient reports at least two of the following:
        i. Straining during at least 25% of defecations
        ii. Lumpy or hard stool in a least 25% of defecations
        iii. Sensation of incomplete evacuation for at least 25% of defecations
        iv. Sensation of anorectal obstruction/blockage for at least 25% of defecations

9. Patients who met the eligibility criteria and EHD compliance criteria also had to demonstrate the following during the 2-week Pre-Treatment EHD symptomatology Assessment Period:
    - Less than three (3) complete spontaneous bowel movements (CSBMs) per week
    - Bristol Stool Form Scale (BSFS) of six or seven in less than 25% of SBMs
    - One out of the following three (a, b, c):
        i. BSFS of 1 or 2 in at least 25% of defecations
        ii. A straining value recorded on at least 25% of days when a BM was reported
        iii. At least 25% of BMs resulted in a sense of incomplete evacuation

A SBM was defined as a BM that occurred in the absence of laxative use within 24 hours of the BM. A CSBM was defined as an SBM with the sense of complete evacuation.

Key Exclusion Criteria

SP304203-00 and -03

Patients were excluded from study participation if they met any the following criteria at the time of the Screening Visit:

1. Major surgery (e.g., requiring general anesthesia) within 60 days
2. Cancer in the past 5 years
3. History of acute or chronic HBV, HCV or HIV infection
4. Alcoholism, drug addiction or significant drug abuse within the last year
5. Cerebrovascular event (stroke) or myocardial infarction (MI) in the last 6 months
    a. History or presence of pseudo-obstruction, colon cancer, malignant polyps, colitis, ischemic colitis, abdominal adhesions, intestinal ischemia, or esophageal atresia
6. History of substantiated diverticulitis
7. Fecal impaction that required hospitalization or emergency room treatment in the last 3 months
8. Eating disorder in the last 5 years
9. Cathartic colon, laxative or enema abuse, intestinal pseudo-obstruction or pelvic floor dysfunction
10. Familial adenomatous polyposis
11. Gastric bypass surgery (at any time) or open surgery of the abdomen, pelvis, or retroperitoneal structures within 6 months, or laparoscopic appendectomy, cholecystectomy, or other instrumentation of the bowel in the last 60 day
12. Patient did not maintain a stable diet for at least 30 days prior to the Screening Visit or was unwilling to maintain a stable diet during the study.
13. Patient had abnormal laboratory results deemed clinically significant by the investigator at the Screening Visit, which prevented patient randomization.
14. Patient had any known medical condition, clinical signs and symptoms, vital signs, abnormal laboratory, or ECG considered clinically significant by the investigator that could interfere with the patient's participation in and completion of the study including, but not limited to:
    a. Undiagnosed (i.e., previously untreated), uncontrolled hypertension defined as systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg on three occasions during the Screening Visit, with each measurement taken after at least five-minutes sitting at rest
    b. Uncontrolled diabetes (defined as hemoglobin A1C [Hgb A1C] > 10% at Screening)

c. Previous anaphylactic reaction to any medication
d. Clinically significant abnormal ECG
e. Patient had a history of adrenal disease, diabetic nephropathy, or gastroparesis
f. Patient had uncontrolled hypothyroidism. (A patient with chronic hypothyroidism was allowed, provided their dose of thyroid hormone replacement had been stable for at least 30 days prior to the Screening Visit and any thyroid stimulating hormone [TSH] elevation or decrease was considered not clinically-relevant by the investigator).

15. Patient had a cerebrovascular event (stroke) or myocardial infarction in the last 6 months.
16. Patient could not participate in the study if, in the opinion of the investigator or sponsor's MM or designee, it was not in the patient's best interest. The rationale for exclusion of the patient was clearly recorded.
17. Patient had plans to travel to a region considered as high risk for developing traveler's diarrhea while participating in the study.
18. Patient was ineligible for randomization if, during the 2-week Pre-Treatment Assessment, he or she failed to complete six of the seven required daily EHD entries in each of the 2 weeks. The patient was considered compliant for the day if they completed the Daily BM diary portion of the Symptom Diary using their EHD.
19. Patient had a central nervous system condition that could cause constipation (i.e., Parkinson's disease, spinal cord injury, multiple sclerosis, Down's syndrome, and others).
20. Patient had ever had any of the following diseases or conditions that were associated with constipation: pseudo-obstruction, Hirschsprung's Disease, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, collagen vascular disease (scleroderma, amyloid), or systemic sclerosis.
21. Patient had active peptic ulcer disease not adequately treated or not stable with therapy.
22. Patient was taking a pharmacologic treatment for GERD/reflux that had not been stable for 15 days before the Screening Visit.
23. Patient had unexplained and clinically significant "alarm symptoms" including non-hemorrhoid lower GI bleeding, iron-deficiency anemia, or weight loss. As noted above, patients with hemorrhoids MAY have been entered into the study.
24. Patient had a history of substantiated (documented by CT scan or hospitalization) diverticulitis, or any ongoing chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, endometriosis, ovarian cysts, or other) that may have been associated with chronic abdominal pain or discomfort and might confound the assessments in this

study during the 2 years prior to the Screening Visit. Patients with diverticulosis may have been entered into the study.

25. Patient has had a fecal impaction that required hospitalization or emergency room treatment within 3 months of the Screening Visit.
26. Patient had a clinically significant finding on colonoscopy performed as required in accordance with the AGA guidelines (with AGA time frames). If polyps were found and biopsied, pathology must have been reviewed as negative for cancer before the patient could be enrolled in the study. This also applied to colonoscopies conducted as part of Screening.
27. Patient used bisacodyl within 72 hours before the first dose of study drug (Day 1, Week 1) to avoid confounding the data collected in the first week of study drug administration, particularly the time to first BM.
28. Patient reported the use of rescue medication (bisacodyl tablets) for > 2 days in either of the two weeks in the Pre-Treatment Assessment Period.
29. Patient reported participation in a clinical study or use of an investigational drug treatment within 30 days of the Screening Visit.
30. Patient had previously participated in a plecanatide study at any time or had been in a linaclotide study within 15 days of the Screening Visit.
31. Patient had a barium enema within 7 days of the Screening Visit. Patient had taken a protocol-prohibited drug within 15 days of the Screening Visit (except for episodic use of antibiotics or opiates) or would not abide by the protocol restrictions regarding use of prohibited drugs.

Reviewer comment: The overall designs of the randomized, DB, PC studies were acceptable in the assessment of efficacy and safety for the treatment of CIC. The 12-week treatment periods were adequate durations of time to assess the efficacy of an investigational agent intended for the chronic treatment of CIC. This design was agreed upon with the FDA prior to the initiation of the trial. The control group is a placebo group, which should allow for optimal interpretation of results. The modified Rome III diagnostic criteria are acceptable for use to identify the target population of patients with CIC. The use of a two-week pretreatment screening assessment is appropriate to ensure compliance and to ensure that baseline symptoms are sufficient to be able to demonstrate a statistically significant difference between the treatment groups and placebo.

The planned enrolled population adequately represented the population of patients with CIC in the U.S. The inclusion and exclusion criteria appear appropriate and there were no unnecessary

patient exclusion factors. These criteria were also similar to a recent NDA for linaclotide which used the Modified Rome II criteria for functional constipation to determine eligibility.

This reviewer agrees with the limitations imposed on the use of the rescue medication prior to the first dose of study drug in order to ascertain that patients have a true diagnosis of CIC. Also, this could ensure that rescue medication did not confound study results in the beginning of the studies.

Dose Selection

SP304203-00 and -03

The doses of plecanatide selected for these studies were 3 mg or 6 mg once daily treatment over 12 weeks. These doses were based primarily on the results of trial SP304203-10, which was a large, multicenter, dose-ranging, 12-week study in patients with CIC. In this trial, doses of 0.3 mg, 1 mg, and 3 mg plecanatide were evaluated. The 3 mg dose showed the greatest statistical significant treatment effect in the primary and secondary endpoints. Secondary endpoints such as frequency of SBMs and CSBMs, stool consistency, straining, time to first BM, and global assessments such as treatment satisfaction showed a dose response without indication of a plateau effect.

Incidence of diarrhea also showed a positive relationship to increasing dose, but diarrhea only increased from 8.4% in the 1 mg plecanatide dose groups to 9.7% in the 3 mg plecanatide dose group. In the phase 2a trial, a higher dose, 9 mg plecanatide, was not associated with more GI side effects as compared with the 0.3 mg, 1 mg, or 3 mg dose groups. The applicant thus selected the 3 mg and 6 mg dose (as a dose lower than 9mg) to study in the phase 3 trials. Please see the Clinical Pharmacology review by Dilara Jappar, PhD for more details.

Reviewer comment: This reviewer finds that the plecanatide 3mg and 6mg doses that were selected for the DB, PC phase 3 studies are acceptable. The 3 mg dose was selected based on the results of the dose ranging study which showed improved efficacy with 3 mg, compared to lower doses. In a previous phase 2a study, 9 mg plecanatide was studied and was not shown to have additional GI side effects. As such, the applicant selected 3 mg and 6 mg for their phase 3 study.

Study Treatments

SP304203-00 and -03

Patients who met eligibility criteria were randomized in a 1:1:1 fashion to 1 of the 3 treatment groups using the Randomization and Trial Supply Management (RTSM) system to receive a single daily oral dose of placebo, 3 mg plecanatide, or 6 mg plecanatide (all tablet formulations) for 12 weeks. Patients were to take one tablet daily, in the morning, with approximately 8 ounces of water.

1) Group 1: plecanatide 3 mg oral tablets QD
2) Group 2: plecanatide 6 mg oral tablets QD
3) Group 3: matching placebo oral tablets QD

The drug product is a tablet comprised of plecanatide, microcrystalline cellulose, and magnesium stearate. The matching placebo composition is identical but does not contain plecanatide.

Assignment to Treatment

SP304203-00 and -03

At the Day 1, Week 4, and Week 8 Visits, the investigators performed real-time randomization via the Interactive Web Response System (IWRS). Drug dispensing activities were performed by logging into the Randomization and Trial Supply Management (RTSM) system for study drug kit allocation for each patient. The treatment type was defined by the treatment allocation at the randomization visit (Day 1). Consignments for additional kits were generated as kits were dispensed and the RTSM system managed inventory and anticipated the needs of the site based on the number of patients enrolled.

A unique 6-digit patient number was assigned by the site consecutively for each patient after each patient signed the informed consent. The unique patient numbers were given sequentially by clinical site personnel. The patients kept this unique patient number for the duration of the study. Patients who discontinued from the study before randomization retained their unique patient number and numbers from screen fail patients were not reassigned.

Patients received their assigned study drug on the day of randomization, Day 1 of Week 1, and took their first dose at the clinical site.

Each investigational drug kit contained a 4-week supply in blister packaging including four extra tablets for a total of 32 tablets. This extra supply was to allow for a 3-day window to return for a study visit. On Day 1, the patient received one blister pack folder for the first 4 weeks of dosing (Weeks 1, 2, 3, and 4). All doses thereafter were taken at home once daily at approximately the same time in the morning with 240 mL (~8 oz.) of water. Patients were allowed to take study drug with or without food at their own choice. On Weeks 4, 8, and 12 (each ± 3 days), patients returned to the clinic to undergo safety and efficacy assessments. At the Week 4 and Week 8 Visits (each ± 3 days) patients received a new blister pack folder for Weeks 5 to 8 and Weeks 9 to 12 of dosing, respectively. Patients were instructed to return their kits at each study visit to allow determination of compliance and reconciliation of supplies. Treatment compliance was assessed at the study centers by pill count.

Blinding

SP304203-00 and -03

The study was performed in a double-blind manner. All patients, investigators, and the study site personnel were unaware of the patient treatment assignments. Assuring double-blind conditions, all study drugs were supplied in identical blister packs and tablets was similar in color, smell, taste, and appearance. In the event of a treatment emergency, the investigator, all sub-investigators at the clinical site, and the sponsor's Medical Monitor (MM) was granted emergency code-break privileges using the RTSM. The time, date, reason, name and signature of the person responsible for any break in the code was to be fully documented in the patient's source documents and any associated AE recorded.

Dose Modification/ Dose Discontinuation

SP304203-00 and -03

For these studies, there were no dose modifications or reductions pre-specified in the protocol.

Dietary Restrictions/ Instructions

SP304203-00 and -03

A stable dietary intake of high fiber, fiber supplements, vitamins and minerals, probiotics, and fish oil was required during the study. Patients were required to be on a stable dietary regimen for 30 days before the start of the 2-week Pre-Treatment electronic diary assessment and needed to remain on that diet, including all supplements, for the duration of the study.

Prior and Concomitant Medications

SP304203-00 and -03

At the Screening Visit, patients gave requested details about traditional and non-traditional medications that they took during the last 30 days. Any medication that the patient consumed other than the study drug was considered a concomitant medication. Throughout the study, the patients were asked about taking concomitant medications. The use of rescue medication, as given per the sponsor, was recorded daily by the patient and was not considered to be a concomitant medication.

Prohibited Concomitant Medications

Certain types of medications were prohibited 15 days prior to the Screening Visit and for the duration of the study unless otherwise indicated. All washout and stabilization of concomitant medications had to be completed before the start of the 2-week (15 days) EHD Pre-Treatment assessment that established baseline data for the patient. Prohibited medications included all medications and herbal therapies used to treat constipation or facilitate BMs, and previous plecanatide treatment. Other prohibited medications, laxatives, and supplements) included:

1) Antibiotics, including rifaximin; episodic use of antibiotics during treatment was permitted for up to a total of 15 days
2) Oral anticholinergic agents (topical and inhaled anticholinergics were allowed)
3) Drugs with activity at the 5-HT4, 5-HT3, 5-HT2b receptors, however, antidiarrheal agents including Pepto Bismol, kaolin, and opiates
4) Drugs known to cause diarrhea, such as orlistat, acarbose, misoprostol, and colchicine
5) Bile acid sequestrants (cholestyramine, colestipol)

6) Opioids, including tramadol or opiate anti-diarrheals (diphenoxylate, loperamide); short-term (<15 days) use of opioids was permitted during the treatment period
7) Amitiza® (lubiprostone) (15-day washout needed)
8) Lactulose (3-day washout needed)
9) Linzess®/ Constella® (linaclotide) (15-day washout needed)
10) Resolor® (prucalopride) (15-day washout needed)

All laxatives (except for Rescue Medication [RM]) as described below were prohibited from 72 hours before the 2-week EHD Pre-Treatment assessment and onward for the duration of the study (including 2 weeks post-treatment). Prohibited laxatives included the following:

1) Lactulose
2) Stimulant laxatives including senna and sennosides, cascara sagrada,
a. anthraquinones, castor oil, aloe, or other
3) Osmotic laxatives (e.g., polyethylene glycol 3350, magnesium hydroxide,
a. magnesium sulfate sodium biphosphate, saline laxatives [magnesium citrate], glycerine suppositories, glucitol, lactulose
4) Bisacodyl other diphenylmethane laxatives (phenolphthalein)
5) Stool softeners (docusate sodium)

The following drugs were allowed only if the patient was on a stable dose for the 15 days prior to the 2-week Pre-Treatment baseline and the patient agreed to remain on this dose for the duration of participation in the study:

1) Anticonvulsants
2) Antidepressants
3) Calcium channel blockers
4) Proton pump inhibitors and H2 antagonists
5) Antihistamines that have primarily anti H1 activity (e.g., cetirizine, loratadine, chlorpheniramine)
6) Bulking agents (e.g., psyllium [Metamucil®] methylcellulose [Citrucel®], calciumpolycarbophil)

Thyroid hormone supplementation with levothyroxine (T4), natural desiccated thyroid hormone, or liothyronine (T3) were allowed only if the patient was on a stable dose for the 30 days prior to the 2-week Pre-Treatment baseline and remained on this dose for the duration of participation in the study.

Use of short-term opioids or antibiotics (≤15 days) for the treatment of AEs or inter-current illness were allowed. Short-term use could occur during the Screening Period prior to the 2-week EHD Pre-Treatment baseline or after randomization in the study as long as they were reported. If a patient was started on an antibiotic or a narcotic during the Screening Period, their 2-week Pre-Treatment baseline may have been delayed to allow them to discontinue these medications at least 3 days before their 2-week EHD entries.

Patients who were undergoing a colonoscopy during the Screening Period were allowed to take laxatives, enemas, and/or stool softeners only as part of the colonoscopy preparation procedures. A ten-day period was required after a colonoscopy before the patient was randomized. Prohibited drugs used to treat TEAEs were allowed.

Rescue Medication

SP304203-00 and -03

The only rescue medication (RM) for constipation allowed for use in these studies was Dulcolax® (bisacodyl) 5 mg. As needed, Dulcolax® was supplied as rescue medication and dispensed at the end of the Screening visit on Day 1, Week 4, Week 8, and/or Week 12 visits. Patients were instructed to take one or two tablets only if at least 72 hours (at least) had elapsed since their last BM. Patients were recommended to have no more than 2 days of RM use per week.

The use of RM was restricted to 4 days during the Pre-Treatment Period which was equivalent to no more than 2 days of RM use during each of the two pre-treatment weeks. Rescue medication could not be taken for 72 hours before or after randomization to allow determination of an accurate time to first BM. Subsequently, when patients were seen monthly they were expected to have had no more than 8 days of use between visits, depending on visit windows. Patients reported when they took rescue medication and how much they took via their EHD as part of their Daily BM Diaries. However, supplies of bisacodyl were not reconciled at the completion of the study.

Administrative Structure

SP304203-00 and -03

Please see Table 74 in the Study Administrative Structure in the appendix.

Procedures and Schedule

SP304203-00 and -03

The schedule of events and the study procedures for the prescreening and screening period is provided in the Table 5 below for both Studies -00 and -03.

Table 5: Trial SP304203-00 and -03 Schedule of Events and the Study Procedures

Study Period	Screening[a]		Treatment				Post-Treatment	
Visit	Screening-1	Screening-2 Pre-Treatment	Week 1	Week 4	Week 8	Week 12 (EOT)	Week 14 (EOS)	Early Withdrawal
Visit (Window) Days	0 to 4 weeks Start Pre-Treatment		Day 1 within 4 days of end of Screening	Day 28 ± 3	Day 56 ± 3	Day 84 ± 3	2 weeks after DOPV ± 3	Within 5 days of withdrawal
Informed Consent	X							
Inclusion/Exclusion Criteria	X		X					
Medical History (GI and Bowel Habits/ Demographics)	X		X					
Colonoscopy[b]	X							
Prior and Concomitant Medications/Diet	X		X	X	X	X	X	X
Physical Examination[c]	X		X	X	X	X	X	X
Vital Signs[d]	X		X	X	X	X	X	X
Pregnancy Test[e]	X	X	X			X	X	X
Serum Chemistry, Hematology, Urinalysis[f]	X		X	X	X	X	X	X
Immunogenicity serum testing[g]			X	X			X	X
UDS for Opioids[h]	X	X	X					
12-Lead ECG[i]	X		X			X		X
Train on EHD/Review Response[j]	X	X	X	X	X	X		
Randomization			X					
Study Drug Administration[k]			X					
Study Drug Dispensed[l]			X	X	X			
Study Drug Collection and Accountability				X	X	X	X	X
Rescue Medication Supply/Resupply[m]	X		X	X	X	X		
Daily BM and Symptom Diaries (EHD)[n]	X	X	X	X	X	X	X	X
PAC-QOL©, PAC-SYM©, PGA Questionnaries[o]			X	X	X	X	X	X
Adverse Events[p]	X	X	X	X	X	X	X	X

Source: Table 4, Applicant SP-301203-00 Clinical Study Report Body; BM = bowel movement, BMI = body mass index, DOPV = day of previous visit, DRE = digital rectal examination, ECG = electrocardiogram, EOT = End of Treatment, EOS = End of Study, EHD = electronic hand-held device, EW = Early Withdrawal, FSH = follicle stimulating hormone, GI = gastrointestinal, hr = hour, PAC = Patient Assessment of Constipation, PE = physical examination, QOL = Quality of Life, SYM = symptom, PGA = Patient Global Assessment, UDS = urine drug screen, US = United States

SP304203-03: Additional Schedule of Events and the Study Procedures: Intensive PK Sampling

Study SP304203-03 also included PK endpoints with a PK sub-study of plasma plecanatide and SP-338 (the major plecanatide metabolite) assessments in 95 patients: 31 patients from the 3 mg plecanatide group, 32 patients from the 6 mg plecanatide group, and 32 from the placebo group. Samples were collected from patients randomized to all treatments to maintain comparable trial conditions and the study blinding, but only samples from patients randomized to active treatment were analyzed. Samples were collected from patients randomized to all treatments to maintain comparable trial conditions and the study blinding, but only samples from patients randomized to active treatment were analyzed. No placebo samples were analyzed. f the plasma concentration of plecanatide was not quantifiable after 8 hours, the 12, 24 and 72 hour samples were not assayed. See Table 6 below for the scheduled of the PK assessments.

Table 6: SP304203-03 Study Schedule of PK Assessments (Selected Sites Only)

Intensive PK Sampling Time Points										
	Week 4 – Nominal Time (Hr)								Day 29	Day 31
	0	0.5	1	2	3	4	8	12	24	72
Plasma sample collection for plecanatide and major degradant (SP338) PK[a]	X	X	X	X	X	X	X	X	X	X

Source: Sponsor's Study SP304203-03 Protocol pg. 33/88
Hr = hour, PK = pharmacokinetic; a. Note: At selected sites, intensive PK sampling was performed at the Week 4 Visit pre-dose, at the time points indicated in the table and at PK visits scheduled for 24 and 72 hours after the Week 4 Visit. Plasma samples were collected from patients at the sites that consented to the added procedures, with the enrollment target of approximately 30 patients (10 per dose arm).

Prescreening and Screening Period (up to 51 days):

During prescreening and the following the signing of the informed consent document, patients began prescreening evaluations and procedures. The investigator assessed all inclusion/ exclusion criteria to determine patient eligibility, with exception of those related to EHD criteria. All evaluations were intended to be completed in one day for patients who did not require colonoscopy, washout of a prohibited medication, or stabilization of diet or a medical condition. If the patient requires stabilization, washout,

or colonoscopy the patient completed the balance of screening requirements at a second scheduled Screening Visit.

Patients who remained eligible were given an EHD after the first sets of required screening evaluations and wash out periods were completed. The EHD was used to complete two weeks of daily diary entries as part of a Pre-Treatment EHD Screening assessment.

During the Pre-Treatment Period, patients completed daily assessments of bowel movements in the Daily BM Diary, and symptoms in the Daily Symptom Diary, using the EHD and also recorded the amount of rescue medication (Dulcolax® 5 mg tablets) taken.

This 2-week Pre- Treatment Period was intended to confirm eligibility, confirm ability to comply with study procedures, and establish each patient's baseline values for primary and secondary endpoints, prior to randomization.

For this reason, the RTSM and EHD systems were integrated and programmed to review and evaluate the following EHD data to confirm eligibility for study participation. Only patients who meet the modified ROME III criteria and demonstrate diary and RM compliance are eligible to participate in the study by reviewing the following:

1) The Pre-Treatment Daily BM and Daily Symptom diaries to ensure patients have completed 6 of the 7 days of BM Diary entries in each of the 2 weeks of Pre-Treatment EHD assessments
2) Data to ensure that Rescue Medication was not used more than 2 days during either of the two pre-treatment weeks
3) Bristol Stool Form Scale (BSFS) scores to ensure the patient has scores of 6 or 7 for < 25% of defecations. Review BMs to ensure < 3 CSBMs in each of the 2 Pre-Treatment weeks.
4) BMs to ensure one out of the following three over the two-week treatment period: (1) BSFS of 1 or 2 in at least 25% of defecations, (2) a straining value recorded on at least 25% of days when a BM was reported; (3) at least 25% of BMs result in a sense of incomplete evacuation

Treatment Period

SP304203-00 and -03

Patients who were eligible at the end of the Screening Period were stratified by gender then randomized in a 1:1:1 ratio to one of the following three treatment groups: 3 mg plecanatide, 6 mg plecanatide, or placebo. They received their assigned study drug on the day of randomization (Day 1 of Week 1) and took their first dose at the clinical site. Patients continued to take a single oral dose of study drug once daily for 12 weeks.

At Weeks 4, 8, and 12 (each ± 3 days), patients returned to the clinic to undergo safety and efficacy assessments. Supplies of study drug were replenished at the Week 4 and Week 8 Visits. Unused study drug from the previous visit was collected. At select visits (Week 1, 4, 14 or at early withdrawal), blood samples were obtained for immunogenicity testing for anti-plecanatide antibodies before patients received their first dose of study drug at the clinic.

At the end of the 12 weeks of study drug administration (±3 days), patients returned to the clinical site for End of Treatment (EOT) safety and efficacy assessments. At the end of the 2-week Post-Treatment Period, they returned for End of Study (EOS) efficacy and safety assessments. Patients continued to complete daily EHD diaries throughout the Treatment and Post-Treatment Periods.

Post-Treatment Follow-up (Week 14 or End of Study)

Patients who completed the study through week 12 were to return to the clinic for a post-treatment follow-up assessment. The schedule of events and the study procedures for the post-treatment follow up are included in the Table 5 above.

Treatment Compliance

SP304203-00 and -03
A patient was considered compliant for the studies if they met the definitions of EHD compliance, treatment compliance, and completed the entire study including the End of Study Visit. EHD compliance (i.e., diary compliance) and overall study compliance was also

calculated. EHD compliance meant that a patient made diary entries for at least 4 of each 7 days in a study week. Patients were considered noncompliant for EHD diaries if they had less than 4 days of diary entries for more than 2 of the 12 treatment weeks. A patient was considered compliant with study treatment if the treatment compliance calculated was equal to or greater than 80%.

Treatment compliance was defined by the dosing compliance ratio:
The number of doses actually taken by the patient ÷ by the number of doses that were expected to be taken during the same period x 100.

Subject Completion, Discontinuation, or Withdrawal

SP304203-00 and -03
Patients were free to withdraw from participation in the studies at any time. Investigators could choose to discontinue a patient's participation in the studies if they believe it was in the patient's best interest clinically.

The following qualify as AEs for which patient participation could have been terminated:

1) A positive pregnancy test
2) Changes in laboratory values, physical exam findings or other assessments considered by the Investigator (or designee) to be clinically significant
3) Clinically significant TEAEs including clinically significant laboratory test abnormalities or SAEs regardless of relatedness to study treatment that caused the patient, investigator or sponsor to feel it is not in the patient's best interest to continue
4) A patient could also be withdrawn from study drug/study by the Sponsor, Regulatory Authorities, or the Institutional Review Board (IRB)

Patients who discontinued early from the study, if possible, had an Early Termination Visit which was to have taken place as soon as possible (and within 5 days) after the patient stopped taking study drug. In all cases, the reason(s) for withdrawal, and the primary reason, were recorded on the electronic CRF (eCRF). Patients withdrawn after randomization were not replaced.

Study Endpoints

SP304203-00 and -03: Primary Efficacy Endpoint

The primary endpoint was the proportion of patients who were considered to be durable overall complete spontaneous bowel movement (CSBM) responders over the 12-week treatment period.

CSBM weekly responder was defined as a patient who had ≥3 CSBMs per week and an increase from baseline of ≥1 CSBM for that week.

Durable overall CSBM responder was a patient who was a weekly responder for at least 9 of the 12 treatment weeks, including in at least 3 of the last 4 weeks.

Reviewer comment: The primary endpoint definition of an overall CSBM responder was agreed upon by the Agency with the sponsor and is noted in the preliminary meeting responses dated July 30, 2013, which were provided for an End of phase 2 meeting. This primary endpoint is the similar to the primary endpoint assessed in the linaclotide placebo-controlled, phase 3 studies in CIC which required patients to be weekly responders for 9 of 12 weeks. Note that while the sponsor proposed the term (b) (4) *be included in the labeling. The term* (b) (4) *was removed by the FDA review team since this was not included in the Pre-IND discussions. Labeling negotiations are ongoing at the time of this review.*

Secondary Efficacy Endpoints

SP304203-00 and -03:

1. Change from baseline in frequency rate of CSBMs
2. Change from baseline in frequency rate of SBMs
3. Change from baseline in stool consistency based upon the BSFS
4. Change from baseline in Straining Score
5. Treatment satisfaction
6. Patient reported symptoms associated with constipation in the Daily Symptom Diary

Additional Efficacy Endpoints

1. Time to first SBM and CSBM
2. Percentage of patients with SBMs and CSBMs within the first 24 hours
3. Days of Rescue Medication (RM) use
4. Patient Assessment of Constipation Symptoms (PAC-SYM©) Questionnaire
5. Patient Quality of Life (PAC-QOL©) Questionnaire
6. Patient Global Assessments

Other clinically important changes detected in laboratory tests, vital signs, electrocardiograms (ECGs), or physical examinations were reported.

Description of Endpoints

A. Variables Assessed by Electronic Hand-Held Device (EHD)[14]

1. Daily BM Diary for Bowel Movements and Rescue Medication Use: Patients used the EHD daily to record information related to BMs and rescue medication in the Daily BM Diary.

2. Frequency and Completeness of Bowel Movements: Patients reported the numbers of BMs they experienced in 24 hours, the time of each BM, and the completeness of evacuation in the Daily BM Diary.

3. Stool Consistency using the Bristol Stool Form Scale (BSFS): Patients were asked to rate their stool consistency according to the BSFS (see the appendix) which was provided to them at the Screening visit and as needed throughout the Treatment and Post-Treatment Period in the form of a laminated card. The BSFS is a validated measure of stool consistency commonly used in clinical trials.

4. Time to First Bowel Movement: The first dose of study drug administered on Day 1 of the Treatment Period at the clinical site and the time of dosing were recorded. Patients

[14] A listing of the EHD questions are located in the Appendix B.

began reporting bowel movements for the treatment period on the day of dosing. The time of the first BM was extracted from the patients' EHD BM diary data and time to first SBM and CSBM, and percent of patients with an SBM or CSBM in the first 24 hours was derived from these data.

5. Use of Rescue Medication: As part of the Daily BM Diary, the patient was questioned concerning the use of provided rescue medication (Dulcolax®), including days of use, time of use, frequency of use, and amount of rescue medication used. Use of rescue medication was used to determine whether a BM was spontaneous, but only this element is part of the primary endpoint. Other aspects of rescue medication use, (e.g. frequency, dose) were secondary endpoints.

6. Daily Symptom Diary for Assessment of Abdominal Symptoms: As part of the EHD Daily Symptom Diary, the patients were questioned concerning abdominal symptoms and abdominal pain including ease of stool passage (straining), abdominal bloating and abdominal discomfort.

B. Variables Assessed by Electronic Tablet at the Study Site

These questionnaires are tablet based and were administered on Day 1 before the distribution of study drug, at each subsequent study visit during the Treatment Period (Weeks 4 and 12) and at the end of the 2-week Post-Treatment Period. Patients will complete the forms electronically at the clinical site and authorized personnel will review them before the patient leaves, to ensure that all questions have been answered.

1. Patient Assessment of Constipation and Global Assessment Questionnaires:
The Patient Assessment of Constipation (PAC) Quality of Life (QoL) and SYM (symptom) questionnaires were developed to standardize patient-reported assessments of constipation over time. The PAC SYM and PAC-QoL assessments tools for evaluating perceived effects of constipation on the patient's daily life and severity of symptoms, respectively (see the appendix for these questionnaires).

a. Patient Assessment of Constipation – Quality of Life (PAC-QoL):
The PAC-QOL questionnaire is made up of 28 questions which assess how the patient has been impacted by constipation over the specified period. The questions

measure worries and concerns, physical discomfort, psychosocial discomfort, satisfaction, and overall effects on the patient's quality of life. Patients will be asked to give their response on a scale of 0 ("not at all" or "none of the time") to 4 ("extremely" or "all of the time").

b. Patient Assessment of Constipation – Symptoms (PAC-SYM):
The PAC-SYM questionnaire is made up of 12 questions addressing specific symptoms of constipation. The patient were asked to rate each symptom on a scale of 0 ("absent") to 4 ("very severe").

2. Patient Constipation Experience: At baseline, at the Day 1 visit, patients were asked two questions on their constipation experience:

(1) What they consider their single most bothersome symptom?
(2) What other treatments have been used?

3. Patient Global Assessment (PGA) Questionnaire: The Patient Global Assessment (PGA) questionnaire is designed to provide a high-level assessment of constipation severity and discomfort before, during, and after treatment. Four different forms of the questionnaire was administered, a Pre-Treatment form (Day 1, Week 1), a Treatment Period form (Week 4 and Week 8 visits), an End of Treatment form (week 12 [EOT] visit), and an End of Study (Week 14 [EOS] visit). All four forms ask the patient to rate constipation severity. The Treatment Period and EOT forms will also measure change in constipation symptoms and treatment satisfaction. The EOT form will also assess the patient's desire to continue treatment.

Statistical Analysis Plan (SAP)

SP304203-00 and -03

Table 7 below describes the types of population analysis sets for both Studies -00 and -03.

Table 7: Trial SP304203-00 and -03 Definition of Analysis Sets

Analysis Set	Definition
Intention-to-treat (ITT)	All unique patients who will be randomized into the study. Patients will be analyzed according to their randomized treatment. This will be the main population for assessment of efficacy.
Per Protocol (PP) Population	All patients in the ITT Population who completed the 12-week Treatment Period or discontinued from study treatment due to reasons of AE(s) or lack of efficacy (insufficient therapeutic response) will be treatment compliant and had no major protocol violations. Decisions regarding exclusion from the PP analysis will be made prior to un-blinding the database. All duplicate patients (index and non-index) will be removed from the PP population as major protocol violators.
Safety	All randomized patients who received at least one dose of the study drug. Patients will be to be analyzed according to the treatment received. All safety analyses will be based upon the Safety Population.

Source: Sponsor's CSR Study SP304203-00 and-03

The efficacy analyses will be based on the ITT population and a secondary analysis will be also performed based upon the PP Population, to assess the sensitivity of the analysis to the choice of analysis set.

Categorical variables will be summarized by the number and percentage of patients in each level. Continuous variables will be summarized by number of observations, mean, standard deviation (SD), median, minimum, and maximum. Summaries will be presented by treatment group (placebo and 3 mg and 6 mg plecanatide) and combined active doses. All eCRF collected and derived data will be listed.

The primary efficacy endpoint will be based on an analysis of the durable overall CSBM responder rates using a Cochran-Mantel-Haenszel (CMH) test stratified by gender. For

each plecanatide group, the proportion of durable overall CSBM responders will be compared to the proportion in the placebo group using the CMH test stratified by gender. The number and percentage of durable overall CSBM responders for each treatment group (and 95% confidence intervals [CI]), the difference in responder rates between each plecanatide group and the placebo group (and 95% CIs), and the two-sided *p*-value associated with the above CMH test were presented.

Methods for imputation of missing data and the analysis population employed will be specified in each analysis. The primary method for imputation of missing diary data used for this study will be the mean replacement approach (MRA). Sensitivity analyses based on alternative missing diary data imputation methods (such as the Multiple Imputation [MI], Observed Cases [OC], and Last Observation Carried Forward [LOCF] methodologies) will be performed on the primary endpoint and the CSBM weekly responder rates by week over the 12-week Treatment Period. The weekly responder rate by week will be analyzed using a separate CMH test, stratified by gender.

Sensitivity analyses based on alternative imputation methods (MI, LOCF, and OC) will be also performed on the change from baseline over the 12-week Treatment Period in CSBM frequency, SBM frequency, straining score, and stool consistency using the linear mixed model analysis as specified for each endpoint.

The planned sample size for this study will be based on results of the previously completed large, multicenter, 12-week dose ranging study of plecanatide in patients with CIC and on consideration of overall safety exposure requirements. The percentage of overall responders used for the calculation will be based only on information regarding the current day's symptoms provided by the patient (i.e., "historic" data provided for "a previous day" will be excluded). The power calculation conservatively assumes that the 6 mg plecanatide overall responder rate will be the same as seen in the 3 mg plecanatide dose group. Using these assumptions, and based on a chi-square continuity-corrected test with the intention of providing approximately 90% power at 5% significance level, enrollment of at least 450 patients per treatment arm will be required.

For study SP304203-03, the PK Population consisted of those randomized patients at selected sites participating in the PK sub-study who received study drug and had at least one post-dose PK assessment completed. The PK Population will be analyzed per treatment received.

Protocol Amendments

SP304203-00

During study SP304203-00, the protocol was amended three times and several additional administrative or minor changes were made. A summary of each amendment is provided below:

Protocol v2.0, dated 03 Oct 2013

The following amendments were made to the original protocol v1.0, dated 09 Aug 2013:

1) The patient diary was changed to reflect that only straining associated with SBMs would be assessed to reflect change to the secondary endpoint of straining.
2) A follicle stimulating hormone assessment was added for post-menopausal females to confirm the post-menopausal state of patient. The change was requested by Schulman IRB and to be consistent with other protocols in the program.
3) A T3 and free T4 test was added for any TSH test that was out of range to allow for interpretation of data.
4) Changes were made to the SAE reporting procedures to clarify that the SAE reporting time clock started when the investigator or site became aware of the event and a statement was added to clarify the reporting of pregnancies.
5) Other changes were minor and administrative and included addition of a reference, correction of spelling errors, clarification of definitions, and correction of inconsistencies.

Protocol v2.1, dated 30 Oct 2013

1) Administrative changes were made to correct minor errors and inconsistencies within the protocol.

Protocol v2.2, dated 19 Nov 2013

1) Administrative change to clarify that the presence of HBV, HCV, or HIV infection would be based on known history and that the investigator would decide what is clinically significant hypertension for patients previously treated.
2) The number of 12-lead ECGs required was changed from every visit to one at Week 1, Day 1 and Week 12.

Protocol v3.0, dated 15 Jan 2014

The following amendments were made to protocol v2.0, dated 03 Oct 2013 (and included administrative changes from v2.1 and 2.2):

1) Modification of text on the diagnostic criteria for CIC and diary requirements to be consistent with other parts of the protocol or previous CIC study.
2) Amendment of urine drug screen (UDS) to include only opioid class of drugs to match the objectives for inclusion and exclusion.
3) Clarification provided for assigning patient numbers.

Protocol v3.1, dated 28 Jan 2014

1) Correction of study numbers cited in the protocol and other typos.
2) Clarification of rescue medication use during the Pre-treatment Assessment.

Protocol v4.0, dated 10 April 2015

1) Removal of (b) (4) for data management, randomization and trial supply management and site contracts; replaced by (b) (4) for data management, (b) (4) for randomization and trial supply management, and (b) (4) for site contracts.
2) Clarification that colonoscopy is not intended to be diagnostic.
3) Change of extension study (SP304203-01) reference to open-label study with a treatment duration of up to 72 weeks.
4) Added treatment of AEs as permitted use of prohibited medications including short term (≤15 days) use of opioids or antibiotics and prohibited medications during the Screening Period prior to the 2-week EHD Pre-treatment baseline or after randomization in the study as long as they were reported.
5) Correction of IBS-C diagnosis (as exclusion) with abdominal pain or discomfort for ≥ 3 days per month (was week) in the last 6 months.
6) Allowance of alternate methods of body temperature measurement (e.g. aural).
7) Provide 30-minute window for ECGs post first dose and clarification that ECG 1 hour post dose was only required at Day 1.
8) Onsite dosing at the Week 4 Visit was removed as no pharmacokinetic assessments were required in this study.
9) Changes to the statistical section of the protocol included use of MRA as the primary method for imputation of missing data and replaced MRA in the list of sensitivity analyses with observed case (previously primary).

10) Reorganized secondary endpoints into secondary and additional and changed terminology from key secondary to secondary.

SP304203-03

During study SP304203-03, the protocol was amended three times and several additional minor or administrative changes were made. A summary of each amendment is provided below:

Protocol v2.0, dated 17 Mar 2014
The following amendments were made to the original protocol v1.0, dated 26 Feb 2014:

1) Since the sponsor decided to limit conduct of the study to be within the US only, the words "multicenter" and "international" were deleted from the protocol title and changed to "National." All references to the "Global CIC Study" and "global" references regarding business partners and safety reporting were removed.
2) As the study was converted to US only, reference was needed to the US supplied Dulcolax only.
3) Minor administrative corrections were made (e.g., spelling, capitalizations, consistency, clarifications, etc) throughout the protocol.
4) As the study was converted to US only, contact information for European partners and a footnote regarding trade names in Europe (Appendix 5 and Appendix 6 of the protocol) were deleted.
5) Duplication of the 15-day washout period in Section 3.3.1 of the protocol was deleted.
6) The method of Randomization and Trial Supply Management (RTSM) was changed to IWRS.

Protocol v2.1, dated 26 Mar 2014
The following amendments were made to protocol v2.0, dated 17 Mar 2014:
1) Updated version number and version date to protocol v2.1, dated 26 March 2014.
2) The following text was deleted from Section 7.1 of the protocol - "(e.g., watery/mushy stool [BSFS score of 6 or 7], with a sense of urgency, etc.)" to avoid confusion with diarrhea (reported as an AE) since an increase from baseline in BM's is an expected effect of plecanatide and would be coded as diarrhea.

Protocol v3.0, dated 23 Apr 2015

The following amendments were made to protocol v2.1, dated 26 Mar 2014:

1) Updated phone numbers of study personnel and vendors.
2) Updated the TOC to reflect reorganized content.
3) Clarification that colonoscopy was not intended to be diagnostic.
4) Change of study design and treatment duration of SP304203-01. Removed: "for one year in the long term extension study." Change to: study with "up to 72 weeks" treatment duration.
5) Exclusion Criterion #26 - Correction of wording to align with Rome III Criteria for IBS-C.
6) Clarification regarding short term (< 15 days) use of opioids or antibiotics and prohibited medications for the treatment of AEs or inter-current illness during the Screening Period prior to the 2-week EHD Pre-treatment baseline or after randomization in the study as long as they were reported.
7) Prohibited drugs to treat TEAEs were allowed.
8) Section 4.3.2 (Laboratory Variables) – Typographical error corrected from Week 16 to Week 14 for EOS Pregnancy Test
9) Allowance of alternate methods of body temperature measurement (e.g., aural). Provided a 30-minute window for performance of the ECG and clarification that the timing for the ECG to be1 hour post-dose was only required on Day 1.
10) Day-1 dosing could occur in the morning or afternoon depending on the time the patient's visit was scheduled.
11) Elimination of Week 4 on-site dosing for non-PK patients. Only PK patients required onsite dosing at Week 4.
12) Changes to the statistical section of the protocol to align with the updated SAP included use of MRA as the primary method for imputation of missing data and to replace MRA from the list of sensitivity analyses with OC (previously primary).

Reviewer comment: *This reviewer finds all of the amendments acceptable and does not believe that they would impact the trial or the analysis of results.*

Data Quality and Integrity: Sponsor's Assurance

SP304203-00 and -03

All data generated by the clinical site personnel were captured electronically at each clinical site using eCRFs. Data from external sources (such as laboratory data) were imported into the database. Once the eCRF clinical data were submitted to the central server at the independent data center, corrections to the data fields were captured in an audit trail. Computerized data check programs and manual checks identified any clinical data discrepancies for resolution. If additional corrections were needed, the responsible monitor or data manager raised a query in the EDC application. The appropriate staff at the clinical site answered queries sent to the site. The name of the staff member responding to the query, and time and date stamp were captured to provide an audit trail. Once all source data verification was complete and all queries were closed, the data manager froze the eCRF page.

Site Integrity Issues: SP304203-03, Sites #362 and #402

As aforementioned, there were two sites in study SP304203-03 that had concerning integrity issues. One of the sites (#402) incurred previous Agency enforcement[15] action and another site (#362) received a written violation.[16] These two sites comprised 30 patients out of the 1337 patients in the ITT population of this study. These two sites were removed from the ITT population and examined separately to evaluate for differences in the results. Accordingly, the sponsor was alerted to this concern during the Mid-cycle communication meeting on July 14, 2016 and was requested to perform key result analysis without these sites in order to compare the results.

Reviewer Comments: This reviewer agrees with the removal of sites #362 and #402 in the evaluation of the efficacy and safety of plecanatide in the studies -00 and -03, due to past study integrity issues.

[15]http://www.accessdata.fda.gov/scripts/SDA/sdDetailNavigation.cfm?sd=clinicalinvestigatorsdisqualificationproceedings&id=1E2A9AIBD59D686CE053554DA8COB073&rownum=126

[16] http://www fda.gov/iceci/enforcementactions/warningletters/2016/ucm493102 htm

6.1.2. Study Results: SP304203-00 and -03

Compliance with Good Clinical Practice

SP304203-00 and -03

The sponsor has provided attestation that these studies were conducted in accordance with accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP). They were also conducted in compliance with the International Conference on Harmonization (ICH) E6 Consolidated Guidance for Good Clinical Practice, and the ethical principles of the Declaration of Helsinki (as amended in 1996).

Each investigator was required to provide a dated Financial Disclosure by Clinical Investigators Form to (b) (4) before the first shipment of study drug. No investigator had a financial interest or arrangement that would ethically preclude his or her participation in the study.

Financial Disclosure

SP304203-00 and -03
The sponsor provided a signed copy of FDA Form 3454 with a list of investigator names from each study. This certified that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Patient Disposition

SP304203-00

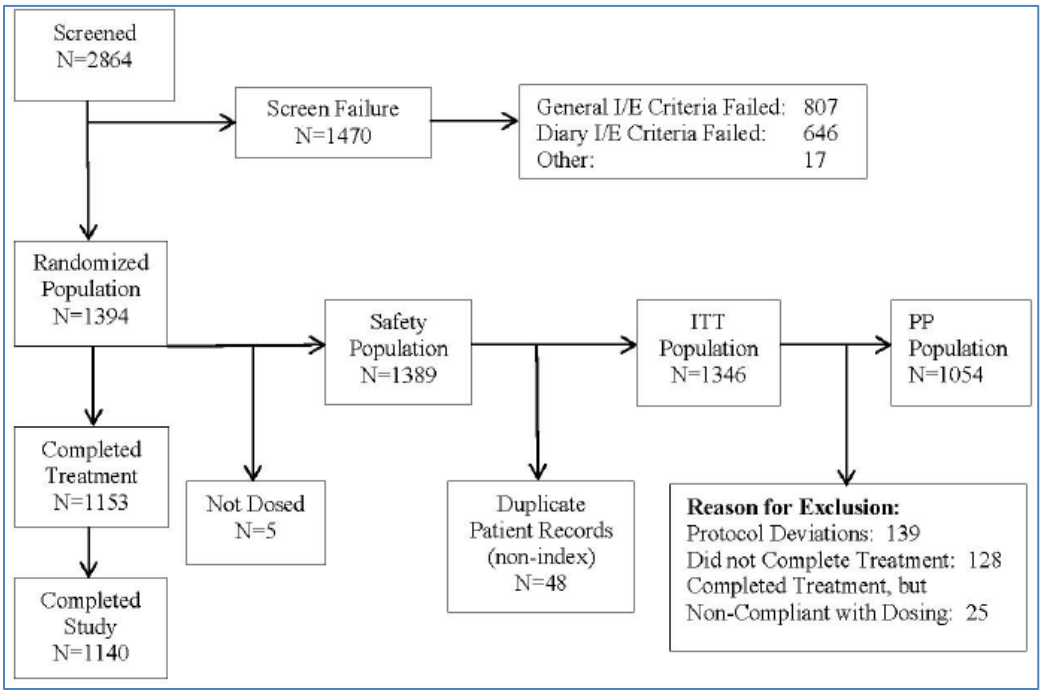
The trial was conducted between Dec 3, 2013 and Apr 23, 2015. A total of 202 study sites were initiated in the US and Canada; of these, 183 were active (i.e., screened patients) and 164 sites enrolled (randomized) 1394 patients.

A total of 2864 patients screened for Study SP304203-00 and 1470 patients failed to meet randomization criteria. The majority of patients (n=807) screen failed because general inclusion and/or exclusion criteria were not met. Additionally, 646 patients failed screening due to ineligibility based on screening/baseline diary entries. Seventeen (17) additional patients screen failed due to a variety of other reasons. Overall, 1394 patients were enrolled and randomized in SP304203-00, including 5 randomized patients who were not treated with study drug after being enrolled in the study.

Duplicated patients were discovered as having participated in one or more study site or in another plecanatide study. Sixty-six (66) unique patients were identified as duplicates and enrolled in this study. Of these, 21 randomized patients were classified as "index cases" (the earliest instance of screening in any study) and were retained in the ITT population. Hence, 48 duplicated cases (3.4 % of the randomized population) were removed from the ITT population.
As such, there were 1346 patients who comprised the ITT population that were derived from the 1394 randomized patients, minus the 48 non-index duplicates and 5 patients who were not dosed.

The PP population (treatment compliant with no major protocol violations) included 1054 patients that were used for sensitivity analysis. Patients who were excluded from the PP population included 139 patients who were excluded for protocol deviations, 128 patients who did not complete treatment, and 25 patients who completed treatment but were non-compliant with dosing. Please see the Figure 3 below for a schematic of the patient disposition.

Figure 3: SP304203-00 Patient Disposition



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

SP304203-03

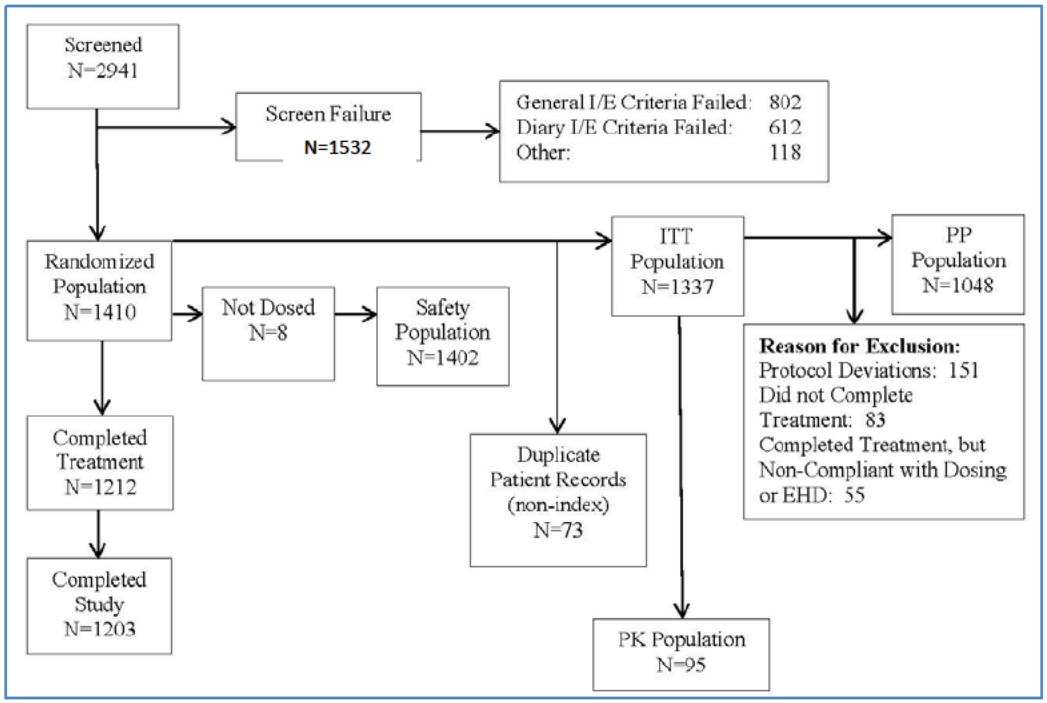
Study SP304203-03 was conducted between May 16, 2014 and May 13, 2015 at 180 study sites. A total of 185 study sites were initiated in the US. Of these, 180 sites actively screened, 162 sites enrolled and randomized a total of 1410 patients. All patients were evenly randomized and stratified (by gender) among the three treatment groups.

A total of 1532 patients screened for Study SP304203-03 failed to meet randomization criteria. The majority (802) screen failed because general inclusion and/or exclusion criteria were not met. Additionally, 612 patients failed screening due to ineligibility based on screening/baseline diary entries; a further 118 patients screen failed due to a variety of other reasons. Overall, 1410 patients were enrolled and randomized in SP304203-03, including 8 randomized patients who were not treated with study drug after being enrolled in the study.

Seventy-three (73) patients were identified as duplicates and non-index cases. The ITT population consisted of 1337 patients, derived from the 1410 randomized patients, minus the 73 non-index duplicates and 8 patients who were not dosed. There were no meaningful differences among the three treatment groups with respect to percentages of patients comprising the PK Population (6.8%, 6.6%, and 6.8%. for the placebo, 3 mg, and 6 mg plecanatide groups, respectively).

The PP population consisted of 1048 patients that were used for sensitivity analysis. Patients who were excluded from the PP population included 151 patients who were excluded for protocol deviations, 83 patients who did not complete treatment, and 55 patients who completed treatment but were non-compliant with dosing. Please see the Figure 4 below for a schematic of the patient disposition.

Figure 4: SP304203-03 Patient Disposition



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

A summary of the analysis populations is shown in Table 8 below for study 304203-00 and -03.

Table 8: Study SP304203-00 and -03 Randomized Patients Disposition

	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[1]	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%)
SafetyPopulation[2]	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
[1] 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)
[2] 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

Reviewer comment: There appears to be a similar percentage of duplicated patients in each study arms. The high number of duplicated patients are concerning, however, it appears that the Applicant worked to address this concern once it was recognized in the trial and it was noticed to occur most often in a handful of sites. There were slightly more duplicated patients in the plecanatide 3mg arm, although the percentage of the patients were small and, reassuringly, only the index cases were included in the ITT population. This aids in ensure the integrity of the study.

Study Discontinuations

SP304203-00

A total of 82.7% of randomized patients completed the treatment phase and 17.3% of patients discontinued the study prior to completion. The most common reasons for discontinuation prior to the

end of treatment were other (4.5%), adverse events (AEs; 3.8%), and withdrawal of consent by patient (3.3%). Twenty-one patients (1.5%) discontinued treatment due to insufficient therapeutic effect: 0.8% in the 3 mg group, 0.7% in the 6 mg group, and 3.0% in the placebo group. Table 9 shows the patient discontinuation per study arm.

SP304203-03

A total of 198 patients (14.0%) were discontinued from study treatment during the 12-week Treatment Period. The incidences of these discontinuations among all randomized patients, including duplicate patients across the three treatment groups, were 12.6%, 16.2%, and 13.4% in the placebo, 3 mg, and 6 mg plecanatide groups, respectively. From the all randomized population (1410 patients), 86.0% of patients completed the treatment phase. The most common reasons for discontinuation prior to the end of treatment were withdrawal of consent by patient (4.4%), protocol violation (3.5%), and AEs (3.2%). Twelve patients (0.9%) discontinued treatment due to insufficient therapeutic effect: 0.6% in the 3 mg group, 0.2% in the 6 mg group, and 1.7% in the placebo group.

Table 9: Study SP304203-00 and -03 Randomized Patients Discontinuation and Completion Status

	SP304203-00			SP304203-03		
Discontinuation/ Completion Status 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)**
Discontinued from the Study During the Treatment Phase	79 (17%)	81 (17%)	81 (18%)	59 (13%)	76 (16%)	63 (13%)
Completed Study Treatment Phase (Week 12, EOT)	388 (83%)	390 (83%)	375 (82%)	410 (87%)	394 (84%)	408 (87%)
Discontinued from the Study after the Treatment Phase	3 (0.6%)	6 (1%)	4 (0.9%)	4 (1%)	2 (0.45)	3 (0.6%)
Completed the Study (Week 14, EOS)	385 (82%)	384 (82%)	371 (81%)	405 (87%)	392 (83%)	405 (86%)

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

Reviewer comment: *Overall, there are a small percentage of patients who discontinued this study. The percentages of patients who discontinued the study during the treatment phase, due to adverse events, were higher in the plecanatide 3mg (4.9%) and 6mg (5.3%) study arms than in the placebo arm (1.3). The discontinuation due to adverse events were very similar between the 3mg and 6mg dosage arms, while the discontinuation due to insufficient therapeutic effect was approximately three times greater in the placebo group (3%) vs. the arms that received the medication (0.8% for the plecanatide 3mg arm and 0.7% for the 6mg arm). These occurrences are not unexpected and are not likely to impact efficacy results. Although the numbers are small, there were more twice as many patients who were lost to follow-up in the 3mg arm vs. the 6mg arm. Overall, there are no clinically important differences in subject disposition between the three arms of the study.*

Protocol Violations/Deviations

Deviations from the protocol, including violations of inclusion/exclusion criteria were assessed as "minor" or "major" in cooperation with the Sponsor. Major deviations from the protocol resulted in exclusion of a patient from the PP population. Violations identified during the course of the trial resulted in early withdrawal from the study. Major protocol deviations and violations are described in Table 10 and Table 11 below.

Table 10: Trial SP304203-00 Major Protocol Deviations

	Plecanatide 3mg (N=456)	Plecanatide 6mg (N=467)	Placebo (N=471)	Overall (N=1394)
Total Major Protocol Deviations	67	71	61	199
Deviation Category, n (%)				
Diary Eligibility Not Met	4 (6.0)	12 (16.9)	5 (8.2)	21 (10.6)
Duplicate Subject	28 (41.8)	22 (31.0)	19 (31.1)	69 (34.7)
IP Dispensing Error	11 (16.4)	6 (8.5)	11 (18.0)	28 (14.1)
Prohibited Concomitant Medication	3 (4.5)	4 (5.6)	2 (3.3)	9 (4.5)
Randomization Criteria Not Met	14 (20.9)	21 (29.6)	23 (37.7)	58 (29.1)
SAE Reporting	1 (1.5)	0	0	1 (0.5)
Study Drug Compliance	5 (7.5)	5 (7.0)	0	10 (5.0)
Subject Diary Compliance	1 (1.5)	1 (1.4)	0	2 (1.0)
Visit Schedule	0	0	1 (1.6)	1 (0.5)
Patients with More than 1 deviation	3 (0.6)	7 (1.5)	2 (0.4)	12 (0.9)
Total Patients with a Major PD	64 (13.6)	64 (14.0)	59 (12.6)	187 (13.4)

Source: Sponsor's Table from June 2, 2016 IR response; Includes duplicate subjects, PD= protocol deviation

Table 11: Trial SP304203-03 Major Protocol Deviations

	Plecanatide 3mg (N=471)	Plecanatide 6mg (N=469)	Placebo (N=470)	Overall (N=1410)
Total Major Protocol Deviations	74	78	93	245
Deviation Category, n (%)				
Diary Eligibility Not Met	4 (5.4)	8 (10.3)	6 (6.5)	18 (7.3)
Duplicate Subject	36 (48.6)	28 (35.9)	32 (34.4)	96 (39.2)
Gender Stratification	0	1 (1.3)	2 (2.2)	3 (1.2)
IP Dispensing Error	2 (2.7)	1 (1.3)	4 (4.3)	7 (2.9)
Prohibited Concomitant Medication	4 (5.4)	3 (3.8)	9 (9.7)	16 (6.5)
Randomization Criteria Not Met	23 (31.1)	27 (34.6)	32 (34.4)	82 (33.5)
Study Drug Compliance	5 (6.8)	9 (11.5)	4 (4.3)	18 (7.3)
Subject Diary Compliance	0	0	2 (2.2)	2 (0.8)
Visit Schedule	0	1 (1.3)	2 (2.2)	3 (1.2)
Patients with More than 1 deviation	3 (0.6)	6 (1.3)	9 (1.9)	18 (1.3)
Total Patients with a Major PD	68 (14.5)	72 (15.3)	84 (17.9)	224 (15.9)

Source: Sponsor's Table from June 2, 2016 IR response; Includes duplicate subjects and sites #362 and #402; PD= protocol deviation

Reviewer comment: The most common major protocol deviation was for patients who did not meet the randomization criteria. This violation occurred fairly equally among the trial arms. Most of these violations appeared to be minor in terms of affecting the efficacy of the study. Such violations included the violation of the randomizing criteria of patients over the age of 50 who did not have a recorded endoscopic examination at screening and upon randomization or who had a pre-existing medical history, such as Melanosis coli or mild diverticulitis. Fortunately, only a small percentage of protocol violation patients used prohibited concomitant medications, which included Amitiza, stool softeners such as Colace, Magnesium Citrate, Senokot and other laxatives, antibiotics and mediations for constipation mostly during the pre-screening washout period. The sponsor excluded patients with major protocol deviations from the PP analysis and results were consistent with the full ITT population.

Protocol Violations Leading to Study Discontinuation

The Tables below show the types of protocol violations that lead to Study Discontinuation in studies SP304203-00 and SP304203-03. Major protocol deviations, including violations leading to discontinuations are shown in Table 12 and Table 13 below.

Table 12: SP304203-00 Protocol Violations Leading to Study Discontinuation

Protocol Violation (Specify)	Number of EW Patients	Treatment Placebo	Treatment 3 mg	Treatment 6 mg
CIC modified Rome III criteria	3	0	1	2
History of Cancer	1	0	0	1
Abnormal Laboratory Results	1	1	0	0
GI related surgery - Gastric bypass, Gastric band, abdominal, pelvic or retroperitoneal surgery or laparoscopy appendectomy/cholecystectomy	1	0	1	0
Rescue medicine use greater than 2 days	1	0	1	0
Duplicate patient	8	1	3	4
Use of Prohibited Medication	5	2	0	3
Non-Compliance with patient diary	3	0	1	2
Non-Compliance with study procedures	1	1	0	0
Total	24	5	7	12

Source: Sponsor's IR response dated Aug. 24, 2016; EW= Early Withdrawal

Table 13: SP304203-03 Protocol Violations Leading to Study Discontinuation

Protocol Violation (Specify)	Number of EW Patients	Treatment Placebo	Treatment 3 mg	Treatment 6 mg
CIC modified Rome III criteria	3	0	2	1
Major surgery within 60 days	1	0	1	0
Clinically significant medical condition	4	2	0	2
GI related surgery - Gastric bypass, Gastric band, abdominal, pelvic or retroperitoneal surgery or laparoscopy appendectomy/cholecystectomy	1	0	1	0
Clinically significant finding on colonoscopy	1	0	1	0
Rescue medicine use greater than 2 days	1	0	0	1
Duplicate Subject	36	13	13	10
Non-Compliance with patient diary	2	2	0	0
Non-Compliance with study procedures	3	2	0	1
Total	52	19	18	15

Source: Sponsor's IR response dated Aug. 24, 2016; EW= Early Withdrawal

Reviewer comment: It appears that most of the protocol violations that led to discontinuations involved the randomization of patients who did not meet eligibility criteria and recognition of duplicate patients. There were more patients in the plecanatide groups who had protocol violations and discontinued the study than placebo patients, although the numbers are small. These discontinuations are unlikely to have an impact on the efficacy results.

Changes in Planned Treatment Group Assignments

Nine patients from the randomized population received study drug inconsistent with their planned treatment assignment. Seven of the nine incidents occurred at one site where a new coordinator failed to follow proper drug kit assignment instructions. Additionally, in the randomized population, five patients did not receive drug following randomization; three in the placebo group and two in the 6 mg plecanatide group. See the Table 14 and Table 15 below.

Table 14: Study SP304203-00 Misrandomized Patients and Untreated Randomized Patients

No.	Subject Number	Safety Population	Treatment Group Planned (assigned)	Actual Treatment Group	Number of Days of Incorrect Treatment
Subjects Whose Actual Treatment Did Not Match Planned Treatment					
1	084-107	Y	Placebo	3 mg plecanatide	32
2	084-109	Y	3 mg plecanatide	6 mg plecanatide	29
3	084-112	Y	Placebo	6 mg plecanatide	29
4	084-113	Y	6 mg plecanatide	3 mg plecanatide	30
5	084-114	Y	Placebo	3 mg plecanatide	32
6	084-118	Y	Placebo	6 mg plecanatide	22
			Placebo	3 mg plecanatide	26
7	084-122	Y	Placebo	3 mg plecanatide	29
8	629-114	Y	3 mg plecanatide	6 mg plecanatide	30
9	685-107	Y	Placebo	3 mg plecanatide	26
Randomized But Not Dosed					
1	317-113	N	Placebo	Not Dosed	-
2	605-114	N	6 mg plecanatide	Not Dosed	-
3	613-137	N	Placebo	Not Dosed	-
4	714-101	N	6 mg plecanatide	Not Dosed	-
5	736-109	N	Placebo	Not Dosed	-

Source: Sponsor's Study-00 CSR Data Errata 14.4.2 and from IR response dated August 24, 2016

Table 15: Study SP304203-03 Misrandomized Patients and Untreated Randomized Patients

#	Subject Number	Safety Population	Treatment Group Planned (assigned)	Actual Treatment Group
Subject Whose Actual Treatment Did Not Match Planned Treatment				
1	210-217	Y	Placebo	6 mg plecanatide
2	428-207	Y	Placebo	3 mg plecanatide
Randomized but Not Dosed				
1	239-212	N	Placebo	Not Dosed
2	299-213	N	3 mg plecanatide	Not Dosed
3	323-204	N	6 mg plecanatide	Not Dosed
4	330-205	N	Placebo	Not Dosed
5	359-201	N	3 mg plecanatide	Not Dosed
6	427-208	N	6 mg plecanatide	Not Dosed
7	428-207	N	Placebo	Not Dosed
8	429-201	N	3 mg plecanatide	Not Dosed
9	452-207	N	3 mg plecanatide	Not Dosed

Source: Sponsor's Study -03 CSR Data Errata 14.4.2

Reviewer comment: *It is reassuring that the most of the mis-randomized patients in study -00 were confined to one site and that this was recognized by the Applicant. The six patients who*

incorrectly received investigational drug when they were originally assigned to placebo would favor the placebo's results in the efficacy evaluation. In study -03, only 2 patients received plecanatide instead of placebo. The Sponsor's approach to analyzing these patients according to the randomization assignment, instead of by the actual treatment group, appears sound.

Table of Demographic Characteristics

Demographic characteristics were similar across the treatment groups, as shown in Table 16 below.

Table 16: Trial SP304203-00 and -03 Demographics (ITT Population)

	SP304203-00			SP304203-03		
Characteristics n (%)	**Placebo (N=448)**	**Plecanatide 3 mg (N=443)**	**Plecanatide 6 mg (N=434)**	**Placebo (N=432)**	**Plecanatide 3 mg (N=422)**	**Plecanatide 6 mg (N=434)**
Sex						
Male	95 (21%)	84 (19%)	76 (18%)	90 (21%)	92 (22%)	90 (21%)
Female	353 (79%)	359 (81%)	358 (82%)	342 (79%)	330 (78%)	344 (79%)
Age (years)						
Mean (SD)	46.5 (13.9)	45.1 (14.7)	45.0 (13.8)	44.7 (14.5)	45.8 (14.3)	45 (14.4)
Median	46.0	45.0	45.0	44.5	46.0	45.5
Min, Max	18, 78	18, 79	18, 79	18, 80	18, 80	18, 80
Age Group						
≥ 18 - < 65 years	401 (90%)	399 (90%)	398 (92%)	379 (88%)	380 (90%)	382 (88%)
≥ 65 years	47 (10%)	44 (10%)	36 (8%)	53 (12)%	42 (10%)	52 (12%)
Race (n [%])						
American Indian or Alaskan Native	0	2 (0.5%)	5 (1%)	0	0	2 (0.5%)
Asian	13 (3%)	13 (3%)	18 (3%)	14 (3%)	7 (2%)	11 (3%)
Black or African American	106 (24%)	125 (28%)	107 (25%)	88 (20%)	86 (20%)	98 (23%)
Native Hawaiian or Other Pacific Islander	0	2 (0.5%)	1 (0.2%)	3 (0.7%)	0	1 (0.2%)
White/Caucasian	321 (72%)	297 (67%)	296 (68%)	322 (75%)	323 (77%)	313 (72%)
Other	8 (2%)	4 (0.9%)	7 (2%)	5 (1%)	6 (1%)	9 (2%)
Ethnicity						
Hispanic or Latino	128 (29%)	106 (24%)	124 (29%)	245 (57%)	231 (55%)	224 (52%)
Non-Hispanic or Latino	320 (71%)	337 (76%)	310 (71%)	187 (43%)	191 (45%)	210 (48%)

Source: Reviewer's Table, Adapted from Sponsor's September 16, 2016 IR response; Excluding duplicate patients and sites #362 and #402; ITT = Intent-To-Treat, kg = kilograms, Max = maximum, Min = minimum, N/n = number of patients, SD = standard deviation.
Note: Percentages are based on the number of patients in the ITT Population in each treatment group.

Reviewer comment: For both studies, approximately 79% of the ITT population was female and the median age was 46 years. The predominant races were white/Caucasian (69%) and black/African American (26%), and the majority of patients were non-Hispanic or non-Latino (72%). The demographic characteristics of sex, age and race appears to be well matched among the three arms in this study. It appears that the demographics of this study does

represent the population of patients with CIC who seek treatment in the US and Canada. This population of patient with CIC includes a large portion of white and female patients, with declining prevalence in the older age group, as reflected in this study population.

Baseline Gastrointestinal Disorders (GI) History and CIC Symptom Characteristics

Patients in all arms had a similar frequency of having a GI disorders history in the ITT population with 48.5%, 44% and 44 % in the placebo, 3 mg, and 6mg plecanatide arms, respectively. In this population, the highest number of patients suffered from hemorrhoids with of the 27.7% in the placebo group, vs. 23.4% and 21.8% in the 3mg and 6 mg plecanatide groups, respectively and then gastrointestinal reflux disease was the second highest. Baseline CIC Characteristics table below summarizes the baseline CIC symptom characteristics for patients from Studies -00 and -03.

Table 17: SP304203-00 and -03 Baseline CIC Symptom Characteristics

		SP304203-00			SP304203-03		
CIC Efficacy Variables	**Parameters**	**Placebo (N=452)**	**Plecanatide 3 mg (N=453)**	**Plecanatide 6 mg (N=441)**	**Placebo (N=445)**	**Plecanatide 3 mg (N=443)**	**Plecanatide 6 mg (N=449)**
CSBM Weekly rate	**n**	449	453	439	444	439	447
	Mean (SD)	0.39 (0.57)	0.32 (0.51)	0.32 (0.51)	0.31 (0.50)	0.28 (0.55)	0.25 (0.44)
SBM Weekly rate	**n**	449	453	439	444	439	447
	Mean (SD)	2.18 (2.03)	1.97 (1.77)	1.82 (1.82)	1.55 (1.59)	1.79 (2.05)	1.60 (1.66)
Stool Consistency (BSFS) Score	**n**	441	438	422	407	424	419
	Mean (SD)	2.56 (1.11)	2.52 (1.05)	2.59 (1.17)	2.35 (1.09)	2.16 (1.03)	2.28 (1.11)
Straining Score	**n**	445	441	427	435	438	442
	Mean (SD)	2.31 (0.84)	2.30 (0.84)	2.28 (0.90)	2.41 (0.85)	2.45 (0.85)	2.47 (0.88)

Source: Study SP04203-00 and -03 CSRs, Sponsor's Tables 14.2.4.1, 14.2.6.1, 14.2.14.1, and 14.2.12.1
Baseline is the mean number of CSBMs/ SBMs recorded during the 2-week baseline diary assessment period prior to the first dose of the study drug. BSFS: Bristol Stool Form Scale

Reviewer comment: In addition to baseline CIC symptoms shown above, the Applicant provided the incidence of a gastrointestinal disorders history (e.g., hemorrhoids), and the baseline incidence was similar across treatment arms and should not impact results. This reviewer finds that the baseline CIC characteristics are similar among all arms for each parameter. This is reassuring in determining

whether plecanatide is efficacious for the treatment of CIC related signs and symptoms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

An individual patient was considered to be compliant with treatment if that patient's study drug compliance rate was 80% or greater. Analysis of treatment compliance was conducted using the ITT Population. The overall Study Compliance is presented in Table 18 below.

Table 18: Trial SP304203-00 and -03 Patient Overall Study Compliance

	SP304203-00			SP304203-03		
	Placebo (N=452)	**Plecanatide 3mg (N=453)**	**Plecanatide 6mg (N=441)**	**Placebo (N=445)**	**Plecanatide 3mg (N=443)**	**Plecanatide 6mg (N=449)**
Number (%) of patients compliant with study[1]	364 (81%)	358 (79%)	346 (79%)	377 (85%)	348 (79%)	367 (82%)
Number (%) of patients compliant with treatment [2]	443 (98%)	437 (97%)	426 (97%)	441 (99%)	432 (98%)	434 (97%)
Number (%) of patients compliant with EHD diaries [3]	377 (83%)	381 (84%)	358 (81%)	386 (87%)	361 (82%)	381 (85%)

Source: Adapted from Sponsor's Table 14.1.7.2, studies SP304203-00 and -03
Note: Percentages are based on the number of patients in the ITT Population in each treatment group.
[1] A patient will be considered compliant for the study if they meet the definitions of electronic hand-held device (EHD) compliance, treatment compliance, and complete the entire study (i.e., complete the End of Study visit).
[2] Treatment compliance is defined as taking equal to or greater than 80% of the drug doses prescribed.
[3] EHD compliance means a patient made diary entries for at least 4 of each 7 days in a study week. Patients will be considered non-compliant for EHD diaries if they have less than 4 days of diary entries for more than 2 of the 12 treatment weeks.

Reviewer comment: Both studies had an overall high compliance rate among the three arms, including compliance with treatment and the EHD diaries. This reinforces that the results of these studies have integrity and that they provide equal and adequate amounts of information from all of the treatment arms.

Efficacy Results

Primary Endpoint Definition: SP304203-00 and -03

Per the sponsor, the primary endpoint was the following: the proportion of patients who were considered to be "durable" overall complete spontaneous bowel movement (CSBM) responders over the 12-week treatment period.

CSBM weekly responders were defined as patients who had ≥3 CSBMs per week and an increase from baseline of ≥1 CSBM for that week.

Overall CSBM responder were defined as patients who was a weekly responder for at least 9 of the 12 treatment weeks, and an overall CSBM responder was also a weekly responder in at least 3 of the last 4 weeks.

In studies -00 and -03, the analysis of the results determined that the proportion of overall CSBM responders for both the 3 mg and 6 mg treatment groups was statistically superior to placebo over Weeks 1 – 12 (p-value < 0.001), as seen in Table 19 below. For study -00, the proportion of responders for plecanatide 3 mg and 6 mg was 21% and 20%, respectively, compared to 10% of placebo responders. For study -03, the proportion of responders for plecanatide 3 mg and 6 mg was 21% and 20%, respectively, compared to 13% of placebo responders.

Table 19: SP304203-00 and -03 Primary Efficacy Endpoint: Number and Percentage of Overall CSBM Responders, MRA method (ITT Population)

Treatment	Primary Efficacy Endpoint				
	Overall CSBM Responders, n (%)[a] [95% CI][b]	Non-Responders, n (%)[c]	P-value[d]	Treatment Difference [95% CI]	Number Needed to Treat [95% CI]
SP304203-00					
Plecanatide 3 mg (N=453)	95 (21.0%) [17.3, 25.0]	358 (79.0)	< 0.001	10.8% [6.1%, 15.4%]	10 (7, 16)
Plecanatide 6 mg (N=441)	86 (19.5%) [15.9, 23.5]	355 (80.5)	< 0.001	9.3% [4.7%, 14%]	11 (7, 21)
Placebo (N=452)	46 (10.2 %) [7.5, 13.3]	406 (89.8)	-	-	-
SP304203-03					
Plecanatide 3 mg (N=430)	88 (20.5%) [16.7, 24.6]	342 (79.5)	0.003	7.5% [2.6%, 12.4%]	13 (8, 38)
Plecanatide 6 mg (N=440)	88 (20.0%) [16.4, 24.0]	352 (80.0)	0.005	7% [2.2%, 11.9%]	14 (8, 45)
Placebo (N=440)	57 (13.0%) [10.0, 16.5]	383 (87.0)	-	-	-

Source: Reviewer's Table, adapted from Sponsor's Table 14.2.1.1 CSR for study SP304203-00 and IR cover letter and response dated August 24, 2016 tables 14.2.1.1 for studies SP304203-00 and SP304203-03; ITT population had sites #362 and #402 removed from study SP304203-03. a. A 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 ≥ 3 CSBMs for a given week and an increase from Baseline of ≥1 CSBM for that same week, determined using MRA methodology as defined in the statistical analysis plan. b. Clopper-Pearson method. c. Patients missing with respect to the endpoint were scored as non-responders. d. CMH p-value for the comparison of treatment group to placebo, stratified by gender.

Reviewer comment: In both studies, a significantly higher proportion of patients in the plecanatide 3mg and the 6mg treatment arms were CSBM responders compared to the placebo treatment arm. For study -00, the treatment differences may be clinically meaningful with an approximate NNT (≈ 1/ treatment difference) for the plecanatide 3mg

group of 10 patients (range of 7 to 16 patients based on the 95% CI), and 11 patients (range of 7 to 21 patients based on the 95% CI) in the plecanatide 6mg group. For study -03, the treatment differences may be clinically meaningful with an approximate NNT (≈ 1/ treatment difference) for the plecanatide 3mg group of 13 patients (range of 8 to 38 patients based on the 95% CI), and 14 patients (range of 8 to 45 patients based on the 95% CI) in the plecanatide 6mg group.

Results in Study -03 were similar to those for -00 and independently demonstrated a statistically significant treatment difference between plecanatide and placebo. The plecanatide 3 mg group was highly statistically significant (p=0.003) compared to the placebo group in terms of the overall CSBM responder rate using the MRA method of analysis across the 12-week Treatment Period. Similarly, the plecanatide 6 mg group also was highly statistically significant (p=0.005) as compared to the placebo group in terms of patients categorized as overall CSBM responders. The results of this study for the primary endpoint were very similar to the SP304203-00 trial.

These results indicate that plecanatide is an effective treatment of CIC with effects that are sustained over the duration of treatment. Patients with CIC may find plecanatide to be clinically meaningful in aiding to relieve their constipation by increasing the number of CSBM per week and maintaining the relief of constipation. Of note, the study was not powered to detect statistical differences between the 3mg and the 6mg dose arm. Hence, it is unclear whether the 3mg or the 6mg dosage of plecanatide is more effective, though their efficacy appeared similar in this study.

The term (b) (4) *will not be considered for the labeling of plecanatide since the review team believes that this term is promotional. The review team recognizes that the definition of the endpoint, without the term* (b) (4) *implies that the efficacy lasts over time. In addition and was not agreed upon during the discussions of the primary endpoint terminology during pre-NDA meetings.*

Sensitivity Analysis

Table 20 below presents the primary efficacy results using the worse-case scenario for handling missing data for studies -00 and -03. This means that no correction was performed for the missing data.

Table 20: SP304203-00 and -03 Overall CSBM Responders, Worse Case Scenario (ITT Population)

Treatment	Number (%)		
	Overall CSBM Responders, n (%)[a], [95% CI][b]	Non-Responders, n (%)[c]	P-value[d]
SP304203-00			
Plecanatide 3 mg (N=453)	94 (20.8) [17.1, 24.8]	359 (79.2)	<0.001
Plecanatide 6 mg (N=441)	87 (19.7) [16.1, 23.8]	352 (80.3)	<0.001
Placebo (N=452)	46 (10.2%) [7.5, 13.3]	406 (89.8)	-
SP304203-03			
Plecanatide 3 mg (N=430)	87 (20.2%) [16.5, 24.3]	343 (79.8)	0.003
Plecanatide 6 mg (N=440)	87 (19.8) [16.2, 23.8]	353 (80.2)	0.005
Placebo QD (N=440)	56 (12.7%) [9.8, 16.2]	384 (87.3%)	-

Sponsor's IR response dated August 24, 2016, Table 14.2.1.1.1.92 and Table 14.2.1.1.1.93, Excluding sites #362 and #402

Reviewer comment: The sponsor conducted pre-specified sensitivity analyses to assess the impact of missing data using a "worse-case scenario " approach, and the results remained statistically significant. This efficacy of the results are seen also when the use of the Observed Cases (OC) method for handling missing data is employed. Hence, the data handling conventions for the missing data did not impact results for this study. The consistency of these results supports the strength of the overall data and generalizability of the results.

Use of Rescue Medicine (Dulcolax®)

The use of Dulcolax® was provided by the sponsor as a rescue medication (RM) that could be used if patients did not have a bowel movement for at least 72 hours. In both studies, more patients in the placebo group used RM than in the treatment group; additionally, more patients in the plecanatide 6mg arm used more RM than those in the 3mg arm. In Study -00, placebo patients took a RM for a mean of 11.3 days during the course of 12-week Treatment Period. Patients treated with 3 mg and 6 mg plecanatide took RM for a mean of 10.1 and 10.7 days, respectively. Similarly, in Study -03, placebo patients took a RM for a mean of 12.5 days, compared to mean of 0.9 and 10.4 days in the 3mg and 6mg treatment arms, respectively. Table 21 below provides a summary of rescue medication use during the 12-week Treatment period.

Table 21: Trial SP304203-00 and -03 Rescue Medication (Dulcolax®) Usage

Treatment Arm	Number of Patients using Dulcolax® n (%)	Total Number of Tablets Used	Mean (SD) Number of Tablets Used	Mean (SD Number of Days of Use)
SP304203-00				
Plecanatide 3mg (n=453)	178 (40%)	2431	13.7 (20.0)	10.1 (17.8)
Plecanatide 6mg (n=441)	201 (46%)	2984	14.8 (22.6)	10.7 (19.1)
Placebo (n=452)	244 (54%)	3868	15.9 (20.7)	11.3 (18.4)
SP304203-03				
Plecanatide 3mg (n=443)	196 (44%)	2291	11.7 (18.1)	9.9 (17.7)
Plecanatide 6mg (n=449)	197 (44%)	2497	12.7 (21.2)	10.4 (18.1)
Placebo (n=445)	228 (51%)	2841	9.6 (16.9)	12.5 (18.4)

Source: Reviewer's table, Adapted from Sponsor's Tables and figures, data errata, SP3040300; Table 14.2.16.1.
Note: The summary covers rescue medication use reported during the Treatment Period, study weeks 1-12. Includes sites #362 and #402

Reviewer comment: *No additional rescue medications or constipation aids were allowed as concomitant medications in this study. The definitions of the components of SBM and CSBM which comprise the endpoints of the trial exclude the use of Dulcolax® with 24 hours of*

having a SBM/CSBM. Although the patient information for Dulcolax® states this product generally produces bowel movement in 6 to 12 hours,[17] the effect of this medication may continue up to or more than 24 hours. While the use of this rescue medication may have contributed to the production of SBM and CSBM after 24 hours of taking the medication, the Sponsor's definition of a SBM and CSBM is generally acceptable. There was more rescue medication use in the placebo arm than the plecanatide arms, which is to be expected. Of note, slightly more patients in the 6mg vs. the 3mg arm used rescue medication.

Table 22: SP304203-00 and -03 Use of Dulcolax Rescue Medication Sensitivity Analysis

Treatment	Overall CSBM Responder (n, %)	95% CI [%]	p-Value
SP304203-00			
No Rescue Medication Use			
Plecanatide 3 mg (N=230)	49 (21.3%)	[16.2%, 27.2%]	<0.001
Plecanatide 6 mg (N=212)	41 (19.3%)	[14.3%, 25.3%]	0.003
Placebo (N=189)	17 (9.0%)	[5.3%, 14.0%]	-
Rescue Medication Use			
Plecanatide 3 mg (N=223)	46 (20.6%)	[15.5%, 26.5%]	0.004
Plecanatide 6 mg (N=229)	45 (19.7%)	[14.7%, 25.4%]	0.007
Placebo (N=263)	29 (11.0%)	[7.5%, 15.5%]	-
SP304203-03			
No Rescue Medication Use			
Plecanatide 3 mg (N=223)	49 (22.0)	[16.7, 28.0]	0.040
Plecanatide 6 mg QD (N=225)	52 (23.1)	[17.8, 29.2]	0.020
Placebo (N=196)	28 (14.3)	[9.7, 20.0]	-
Rescue Medication Use			
Plecanatide 3 mg (N=220)	40 (18.2)	[13.3, 23.9]	0.042
Plecanatide 6 mg (N=224)	38 (17.0)	[12.3, 22.5]	0.091
Placebo (N=249)	29 (11.6)	[7.9, 16.3]	-

Source: Adapted from Sponsor's IR response June 2, 2016, listing 16.2.6.1.1, 16.2.6.12 SP304203-00 and -03; includes sites #362 and #402

[17] https://www.dulcolax.com/laxatives.html#drug-facts. May 9, 2016.

Review Comments: Since this reviewer was concerned that the use of rescue medicine for the relief of constipation could bias the efficacy results, the review team requested this sensitivity analysis from the sponsor. The results of this sensitivity analysis were generally consistent with the pre-specified primary analysis. All subgroups from both studies continued to show a statistically significant treatment difference, with the exception of the 6mg dose group who used rescue medication in Study -03 (p = 0.09). While these results weren't statistically significant, they continued to favor plecanatide. Given that the study wasn't powered for this subgroup analysis, this reviewer finds these results consistent and supportive of the efficacy of plecanatide, with or without the use of Dulcolax. The use of rescue medication does not appear to act as a cofounder to the results since the proportion of responders remained generally consistent among the treatment arms which supports the strength of the overall results.

Effects in Demographic Subpopulations

See the Integrated Summary of Efficacy section 7.1.3 for additional age, gender and race subpopulations results and analyses. Refer to the Table 23 and Table 24 below for the studies -00 and -03 Subgroup Primary Efficacy Endpoint Analysis.

Table 23: Study -00 Primary Efficacy Endpoint Analysis by Subgroup

Final Study 00 Subgroup	Placebo QD (N=452) n (%,)*		Plecanatide 3 mg QD (N=453) n (%,)*				Plecanatide 6 mg QD (N=441) n (%,)*			
	Durable Overall CSBM Responders n, (%)	Total, n	Durable Overall CSBM Responders n, (%)	Total, n	P-value vs. placebo	Treatment Difference (%) 95% CI	Durable Overall CSBM Responders n, (%)	Total, n	P-value vs. placebo	Treatment Difference (%) 95% CI
Durable Overall Response/Al patients										
Sex										
Male	7(7.4)	95	16(18.8)	85	0.022	0.115 (0.016, 0.213)	20(25.3)	79	0.001	0.179 (0.070, 0.289)
Female	39(10.9)	357	79(21.5)	368	<0.001	0.105 (0.052, 0.158)	66(18.2)	362	0.006	0.073 (0.022, 0.124)
Age Group										
>=18 - <40 years	13(8.7)	150	28(16.0)	175	0.052	0.072 (0.001, 0.142)	20(13.6)	147	0.179	0.049 (-0.022, 0.120)
>=40 - <65 years	27(10.6)	255	54(23.1)	234	<0.001	0.125 (0.059, 0.191)	62(24.0)	258	<0.001	0.136 (0.072, 0.200)
>=65 years	6(12.8)	47	13(29.5)	44	0.043	0.173 (0.010, 0.337)	4(11.1)	36	0.811	-0.018 (-0.159, 0.124)
>=75 years	0	8	2(25.0)	8	0.134	0.250 (-0.018, 0.518)	0	6	NA	NA
Race										
White	35(10.8)	323	63(20.9)	302	<0.001	0.100 (0.043, 0.157)	69(22.8)	302	<0.001	0.122 0.064, 0.180)
Black or African American	7(6.5)	108	28(21.7)	129	<0.001	0.152 (0.067, 0.236)	15(13.9)	108	0.077	0.073 (-0.007, 0.153)
Asian	3(23.1)	13	3(23.1)	13	0.683	-0.072 (-0.413, 0.268)	0	18	0.035	-0.227 (-0.437, -0.017)
American Indian or Alaska Native	0	0	1(50.0)	2	NA	NA	0	5	NA	NA
Native Hawaiian or Other Pacific Islander	0	0	0	2	NA	NA	1(100.00)	1	NA	NA
Other	1(12.5)	8	0	5	0.450	-0.119 (-0.336, 0.097)	1(14.3)	7	>0.999	0.000 (-0.367, 0.367)
Ethnicity										
Hispanic or Latino	22 (16.8)	131	33(29.5)	112	0.019	0.127 (0.021, 0.233)	31(24.0)	129	0.137	0.075 (-0.023, 0.173)
Not Hispanic or Latino	24(7.5)	321	62(18.2)	341	<0.001	0.106 (0.056, 0.156)	55(17.6)	312	<0.001	0.102 (0.050, 0.153)
Region										
United States	45(10.3)	436	93(21.4)	434	<0.001	0.110 (0.062, 0.158)	84(19.5)	430	<0.001	0.092 (0.045, 0.140)
Canada	1(6.3)	16	2(10.5)	19	0.666	0.042 (-0.132, 0.217)	2(18.2)	11	0.243	0.140 (-0.094, 0.373)

Source: Sponsor's IR response dated June 20, 2016. Percentages are calculated based on the number of patients in the subgroup per arm; post-hoc analysis

Table 24: SP304203-03 Primary Efficacy Endpoint Analysis by Subgroup

Final Study 03 Subgroup	Placebo QD (N=445) n (%,)*		Plecanatide 3 mg QD (N=443) n (%,)*				Plecanatide 6 mg QD (N=449) n (%,)*			
	Durable Overall CSBM Responders n, (%)	Total, n	Durable Overall CSBM Responders n, (%)	Total, n	P-value vs. placebo	Treatment Difference (%) 95% CI	Durable Overall CSBM Responders n, (%)	Total, n	P-value vs. placebo	Treatment Difference (%) 95% CI
Durable Overall Response/Al patients										
Sex										
Male	17(17.9)	95	17(17.3)	98	0.921	-0.005 (-0.113, 0.102)	16(16.7)	96	0.823	-0.012 (-0.120, 0.095)
Female	40 (11.4)	350	72(20.9)	345	<0.001	0.094 (0.040,0.149)	74(21.0)	353	<0.001	0.095 (0.041, 0.149)
Age Group										
>=18 - <40 years	13(7.6)	171	19(12.3)	154	0.156	0.047 (-0.018, 0.112)	27(17.3	156	0.007	0.098 (0.026, 0.169)
>=40 - <65 years	39(17.7	220	63(25.6)	246	0.041	0.079 (0.004, 0.153)	54(22.5)	240	0.205	0.048 (-0.025, 0.121)
>=65 years	5(9.3)	54	7(16.3)	43	0.408	0.056 (-0.075, 0.187)	9(17.0)	53	0.248	0.076 (-0.052, 0.204)
>=75 years	1(16.7)	6	0	6	0.386	-0.147 (-0.397,0.103)	0	13	0.386	-0.127 (-0.342, 0.088)
Race										
White	45(13.6)	331	66(19.4)	341	0.044	0.058 (0.002, 0.114)	67(20.7)	324	0.017	0.071 (0.013, 0.128)
Black or African American	10(11.0)	91	20(22.7)	88	0.039	0.115 (0.009, 0.222)	20(19.6)	102	0.114	0.082 (-0.016, 0.180)
Asian	0	14	1(14.3)	7	0.197	0.137 (-0.108, 0.383)	1(9.1)	11	0.292	0.087 (-0.074, 0.247)
American Indian or Alaska Native	0	0	0	0	NA	NA	0	2	NA	NA
Native Hawaiian or Other Pacific Islander	1(33.3)	3	0	0	NA	NA	0	1	0.317	-1.000 (-1.000, -1.000)
Other	1(16.7)	6	2(28.6)	7	0.624	0.127 (-0.192, 0.446)	2(22.2)	9	0.949	-0.013 (-0.274, 0.248)
Ethnicity										
Hispanic or Latino	40(15.7)	254	49(19.9)	246	0.223	0.042 (-0.025, 0.108)	47(20.1)	234	0.212	0.043 (-0.025, 0.111)
Not Hispanic or Latino	17(8.9)	191	40(20.3)	197	0.002	0.112 (0.043, 0.181)	43(20.0)	215	0.002	0.111 (0.044, 0.178)
Region										
United States	57(12.8)	445	89(20.1)	443	0.004	0.073 (0.024, 0.121)	90(20.0)	449		0.072 (0.024, 0.121)
Canada	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Source: Sponsor's IR response dated June 20, 2016. Percentages are calculated based on the number of patients in the subgroup per arm; post-hoc analysis, including sites #362 and #402

Analysis By Per Protocol Population

There were no major differences between the PP and the ITT populations' primary efficacy endpoint results and analysis.

Table 25: Study -00 Primary Efficacy Endpoint Results, MRA approach (PP Population)

	Placebo (N=354)	Plecanatide 3 mg (N=357)	Plecanatide 6 mg (N=343)	Active Combined (N=700)
Durable Overall CSBM Responders, n (%) [1]	41 (11.6)	82 (23.0)	81 (23.6)	163 (23.3)
95% CI (%) [2]	(8.4, 15.4)	(18.7, 27.7)	(19.2, 28.5)	(20.2, 26.6)
Non-Responders, n (%) [3]	313 (88.4)	275 (77.0)	262 (76.4)	537 (76.7)
CMH p-value [4]	-	<0.001	<0.001	-
Odds Ratio (adjusted) [5]	-	0.441	0.422	-
95% CI	-	(0.293, 0.664)	(0.281, 0.636)	-
Difference in Proportions (adjusted) [6]	-	0.113	0.122	-
95% CI	-	(0.058, 0.168)	(0.066, 0.178)	-
Breslow-Day p-value [7]	-	0.918	0.168	-

Source: Sponsor's Table 14.2.1.2, SP304203-00

Table 26: Study -03 Primary Efficacy Endpoint Results, MRA approach (PP Population)

	Placebo (N=353)	Plecanatide 3 mg (N=340)	Plecanatide 6 mg (N=355)	Active Combined (N=695)
Durable Overall CSBM Responders, n (%) [1]	49 (13.9)	77 (22.6)	84 (23.7)	161 (23.2)
95% CI (%) [2]	(10.4, 17.9)	(18.3, 27.5)	(19.3, 28.4)	(20.1, 26.5)
Non-Responders, n (%) [3]	304 (86.1)	263 (77.4)	271 (76.3)	534 (76.8)
CMH p-value [4]	-	0.003	<0.001	-
Odds Ratio (adjusted) [5]	-	0.552	0.523	-
95% CI	-	(0.372, 0.819)	(0.355, 0.771)	-
Difference in Proportions (adjusted) [6]	-	0.087	0.098	-
95% CI	-	(0.030, 0.145)	(0.041, 0.155)	-
Breslow-Day p-value [7]	-	0.219	0.049	-

Source: Sponsor's Table 14.2.1.2, SP304203-03

<u>Reviewer comment:</u> In the PP population analysis, plecanatide remains efficacious and has a statistically significant difference in the primary endpoint results for both plecanatide doses and in both studies. This shows that although there were numerous protocol violations, the removal of these subjects did not change the outcome of the primary endpoint

results. This finding is reassuring to this reviewer that those patients who followed the protocols of the studies proved to have robust data and efficacious results.

Efficacy Results –Secondary Endpoints

The following four endpoints are the descriptions of the results from select, statistically pre-specified secondary endpoints that are under consideration for use in the labeling of plecanatide.

I. Change From Baseline Over the 12 Weeks in CSBM Frequency Rate

In Studies -00 and 03 there was a statistically significant LS mean change from baseline through Week 12 for both doses of plecanatide compared to placebo (<0.001). The LS mean change from baseline over the 12-Week Treatment Period in the placebo group for the Study -00 ITT Population was 1.22 CSBMs, and 2.46 and 2.21 CSBMs for the plecanatide 3 mg and 6 mg treatment groups, respectively. In study -03, similar results were seen. There was a statistically significant difference between placebo and plecanatide 3 mg and 6 mg at Week 1. This difference relative to placebo remained consistent through Week 12 of treatment.

As seen in Studies -00 and -03, both the 3 mg and 6 mg doses of plecanatide showed a highly statistically significant change (p-value < 0.001) from baseline over the 12-week Treatment Period in terms of the CSBM frequency rate compared to placebo. The mean baseline CSBM frequency was evenly represented among the three treatment groups in both treatment groups. See Table 27 below for results for the average change from baseline across the 12-week treatment period in studies -00 and -03.

Table 27: Studies -00 and -03 Change from Baseline in CSBMs/week, Average Across the 12-Week Treatment Period, MRA (ITT Population)

CSBM Overall Change from Baseline - Average Across the 12-Week Treatment Period								
	SP304203-00				SP304203-03			
	Baseline (n)	Mean (SE) Change*	Difference from Placebo (95% CI)	P-Value	Baseline (n)	Mean (SE) Change*	Difference from Placebo (95% CI)	P-Value
Plecanatide 3 mg	453	2.46 (0.15)	1.24 (0.87, 1.62)	<0.001	418	2.34 (0.14)	0.93 (0.58, 1.29)	<0.001
Plecanatide 6 mg	439	2.21 (0.15)	0.99 (0.61, 1.37)	<0.001	432	2.19 (0.14)	0.77 (0.42, 1.13)	<0.001
Placebo	449	1.22 (0.15)	-	-	431	1.41 (0.14)	-	-

Source: Reviewer's Table, adapted from Sponsor's September 16, 2016 IR; Excluding sites #362 and #402, *Linear Mixed-effects Model, Mean (SE) Least Square Change

Reviewer comment: *In Study -00, in comparison to the placebo arm, the plecanatide 3mg and 6mg QD treatment arms proved to have better CSBM results, an average of ~ 1 additional CSBM per week than the placebo group, which were highly statistically significant starting early during treatment at week 1. This efficacy persisted to the end of the Treatment phase as week 12. These results indicate that plecanatide is likely to work early in the course of therapy in producing more frequent CSBM in patients and that tolerance or a decrease in efficacy does not occur with the use of the medication. This reviewer expects that these results may be clinically important in patients who suffer from CIC since plecanatide appears to be an effective medication for increasing the number of CSBM per week. The results for Study -03 were consistent. Please see the COA review by Sarrit Kovacs for additional details and cumulative distribution function (CDF) plots regarding the clinical meaningfulness of this secondary endpoint.*

II. Change From Baseline Over the 12 Weeks in SBM Frequency Rate

For Study -00, the changes from baseline in SBM frequency results were similar. The mean change at Week 12 from baseline for the assessment of SBMs per week was statistically significant for both doses of plecanatide (p-value < 0.001) compared to placebo. The LS mean change from baseline over the 12-Week Treatment Period was 1.21, 3.02, and 3.15 for placebo, plecanatide 3 mg, and plecanatide 6 mg,

respectively. The baseline mean scores for each treatment group were comparable. As expected, the numerical magnitude of change in SBMs was greater than that observed with CSBMs.

Similar to study SP304203-00, in Study -03 the mean change across the 12-week Treatment Period for the assessment of SBMs per week was statistically significant for both doses of plecanatide (p-value < 0.001) compared to placebo. The LS mean change from baseline over the 12-week Treatment Period was 1.50, 2.59, and 2.84 for placebo, plecanatide 3 mg, and plecanatide 6 mg, respectively. The baseline mean scores for each treatment group were comparable. The results for both doses of plecanatide were highly significant for each weekly assessment. As expected, the numerical magnitude of change in SBMs was greater than that observed with CSBMs. See Table 28 below for results for the average change from baseline across the 12-week treatment period in studies -00 and -03.

Table 28: Studies SP304203-00 and -03 Change from Baseline in SBMs/week, Average Across the 12-Week Treatment Period, MRA (ITT Population)

SBM Overall Change From Baseline - Average Across the 12-Week Treatment Period								
	SP304203-00				SP304203-03			
	Baseline (n)	Mean (SE) Change*	Difference from Placebo (95% CI)	P-Value	Baseline (n)	Mean (SE) Change*	Difference from Placebo (95% CI)	P-Value
Plecanatide 3 mg	441	3.19 (0.20)	1.92 (1.43, 2.42)	<0.001	418	2.71 (0.17)	1.18 (0.76, 1.60)	<0.001
Plecanatide 6 mg	453	3.11 (0.20)	1.84 (1.34, 2.34)	<0.001	432	2.85 (0.16)	1.33 (0.92, 1.75)	<0.001
Placebo	452	1.27 (0.20)	-	-	431	1.52 (0.16)	-	-

Source: Reviewer's Table, adapted from Sponsor's September 16, 2016 IR; Excluding sites #362 and #402, *Linear Mixed-effects Model, Mean (SE) Least Square Change

Reviewer comment: *In both studies, patients in the plecanatide group appeared to have an average of at least 1 SBM more per week than patients in the placebo arm. This may represent a clinically meaningful difference in patients who suffer from CIC. Similar to the CSBM results, in comparison to the placebo arm, the plecanatide 3mg and 6mg QD treatment arms proved to have better SBM results which were highly statistically significant starting early during treatment at week 1. This efficacy did not wane over time and persisted to the end of the Treatment phase as week 12. These*

results indicate that the medication is likely to work early in the course of therapy in producing more frequent SBM in patients and that tolerance or a decrease in efficacy does not occur with the use of the medication. Please see the COA review for additional details and cumulative distribution function (CDF) plots regarding the clinical meaningfulness of this secondary endpoint.

III. Change from Baseline Over the 12 Weeks in Stool Consistency

Patients were asked to rate their stool consistency according to the Bristol Stool Form Scale (BSFS), see Figure 5 below.

Figure 5: Bristol Stool Form Scale

Source: Sponsor's CSR SP304203-00 and -03

The BSFS is a validated measure of stool consistency commonly used in clinical trials.[18] There was a statistically significant difference (<0.001) in LS mean change from baseline through Week 12 for both doses of plecanatide compared to placebo in the stool consistency score. The baseline LS mean scores for each treatment group were stratified evenly. The LS mean change

[18] Lewis, SJ, Heaton, KW (1997). "Stool form scale as a useful guide to intestinal transit time", *Scand. J. Gastroenterol* :32: 920-924

from baseline over the 12-Week Treatment Period in the placebo group for the ITT Population was 0.77, and 1.53 and 1.52 for the plecanatide 3 mg and 6 mg treatment groups, respectively. The LS mean difference from placebo in the stool consistency score was 0.76 and 0.75 for the plecanatide 3 mg and 6 mg treatment groups. A statistically significant difference (<0.001) between placebo and each plecanatide treatment group was observed as early as Week 1 and remained through the end of treatment at Week 12. The greatest treatment difference between placebo and plecanatide treatment was observed at Week 1, with a subsequent maintained improvement in the stool consistency score weekly through the end of treatment. See Table 29 for the average change from baseline across the 12-week treatment period in studies -00 and -03.

Table 29: Studies SP304203-00 and -03 Change from Baseline Stool Consistency (BFSF), Average Across the 12-Week Treatment Period, MRA (ITT Population)

Stool Consistency (BSFS) Overall Change from Baseline - Average across the 12-week Treatment Period								
	SP304203-00				**SP304203-03**			
	Baseline (n)	**Mean (SE) Change***	**Difference from Placebo (95% CI)**	**P-Value**	**Baseline (n)**	**Mean (SE) Change***	**Difference from Placebo (95% CI)**	**P-Value**
Plecanatide 3 mg	438	1.53 (0.06)	0.76 (0.61, 0.90)	<0.001	403	1.51 (0.06)	0.63 (0.47, 0.79)	<0.001
Plecanatide 6 mg	422	1.52 (0.06)	0.75 (0.60, 0.89)	<0.001	405	1.52 (0.06)	0.64 (0.49, 0.80)	<0.001
Placebo	441	0.77 (0.06)			394	0.88 (0.06)	-	-

Source: Reviewer's Table, adapted from Sponsor's September 16, 2016 IR, excluding sites #362 and #402, *Linear Mixed-effects Model, Mean (SE) Least Square Change

Reviewer comment: *In both studies, the observed difference in stool consistency is small, although statistically significant, between the intervention and the placebo treatment groups and may provide a clinically meaningful difference. Similar to the aforementioned primary and secondary efficacy results, in comparison to the placebo arm, the plecanatide 3mg and 6mg QD treatment arms proved to have improved stool consistency which were highly statistically significant starting early in the course of therapy. This efficacy did not wane over time and persisted to the end of the Treatment phase as week 12. These results indicate that the medication is likely to work quickly in producing improved stool consistency in patients and that tolerance or a decrease in efficacy does not occur with the use of the medication. Please see the COA review for additional details and cumulative*

distribution function (CDF) plots regarding the clinical meaningfulness of this secondary endpoint.

IV. Change from Baseline over the 12 Weeks in Straining Scores

In both studies, there were statistically significant LS mean change from baseline through Week 12 for each dose of plecanatide compared to placebo in the straining score indicative of overall less bowel movement straining due to plecanatide treatment. A statistically significant difference (<0.001) between placebo and each plecanatide treatment group was observed weekly and as early as Week 1 and remained consistent through the end of treatment at Week 12. See Table 30 below for results for the average change from baseline across the 12-week treatment period in studies -00 and -03.

Table 30: Studies SP304203-00 and -03 Change from Baseline in Straining Score, Average Across the 12-Week Treatment Period (ITT Population)

Straining Score Overall Change from Baseline - Average across the 12-week Treatment Period								
	SP304203-00				SP304203-03			
	Baseline (n)	Mean (SE) Change*	Difference from Placebo (95% CI)	P-Value	Baseline (n)	Mean (SE) Change*	Difference from Placebo (95% CI)	P-Value
Plecanatide 3 mg	453	-0.92 (0.04)	-0.35 (-0.45, -025)	<0.001	417	-0.87 (0.04)	-0.24 (-0.35, -0.14)	<0.001
Plecanatide 6 mg	441	-0.88 (0.04)	-0.30 (-0.40, -0.25)	<0.0001	427	-0.90 (0.04)	-0.28 (-0.38, -0.17)	<0.001
Placebo	452	- 0.57 (0.04)	-	-	422	-0.62 (0.04)	-	-

Source: Reviewer's Table, adapted from Sponsor's September 16, 2016 IR, excluding sites #362 and #402, *Linear Mixed-effects Model, Mean (SE) Least Square Change

Reviewer comment: In both studies, similar to the stool consistency results, the observed difference in the change from baseline in straining scores is small, although statistically significant, between the plecanatide and the placebo treatment arms. Since straining with

stooling is a common symptom of many patients with CIC, patients who experience slightly less straining during stooling may perceive this change as clinically meaningful. The improvement in stool consistency in the plecanatide versus. the placebo treatment arm may contribute to the decrease in the straining score that is seen in the plecanatide arms.

Similar to the aforementioned primary and secondary efficacy results, in comparison to the placebo group, the plecanatide 3mg and 6mg QD treatment groups had improved straining scores which were highly statistically significant starting early in the course of therapy. This efficacy did not wane over time and persisted to Week 12 of the Treatment phase. These results indicate that the medication is likely to work quickly in producing improved straining scores in patients and that tolerance or a decrease in efficacy does not occur with the use of the medication. Please see the COA review for additional details and CDF plots regarding the clinical meaningfulness of this secondary endpoint.

Additional Secondary Endpoints

V. Patient Global Assessments (PGA)

The PGA was designed to provide a high-level assessment of constipation severity and discomfort before, during, and after treatment. Included in this scoring system, among other measurements were constipation severity and change in constipation symptoms. Four different forms of the questionnaire were administered, a Pre-Treatment form (Day 1, Week 1), a Treatment Period form (Week 4 and Week 8 visits), an End of Treatment form (week 12 [EOT] visit), and an End of Study (Week 14 [EOS] visit). All four forms asked the patient to rate constipation severity. The Treatment Period and EOT forms also measured change in constipation symptoms and treatment satisfaction. The EOT form assessed the patient's desire to continue treatment. Please see the Figure 6 below for the Week 1, 4, and 8 questions.

Figure 6: Patient Global Assessment (PGA) Questionnaire (segment)

PRE-DOSE Patient Global Assessment Questionnaire (Day 1, Week 1)

Constipation Severity

How would you rate the severity of your constipation at its worst in the past 24 hours?
1= none
2 = mild
3 = moderate
4 = severe
5 = very severe

Patient GLOBAL ASSESSMENT (PGA) QUESTIONNAIRES *continued*
POST-DOSE Patient Global Assessment Questionnaire (Week 4 and Week 8)

Change in Constipation

Since the time you first started taking study medication, how would you describe the change (if any) in your constipation?
1 = very much improved
2 = much improved
3 = minimally improved
4 = no change
5 = minimally worse
6 = much worse
7 = very much worse

Constipation Severity

How would you rate the severity of your constipation at its worst in the past 24 hours?
1 = none
2 = mild
3 = moderate
4 = severe
5 = very severe

Treatment Satisfaction Assessment

Overall, how satisfied are you with the study medication's ability to relieve your constipation symptoms?
1 = Not at all satisfied
2 = A little satisfied
3 = Moderately satisfied
4 = Quite satisfied
5 = Very satisfied

Source: Sponsor's Protocol SP304203-00 and -03

For both Studies -00 and -03, for the constipation severity assessments at Weeks 4, 8, and 12, both doses of plecanatide demonstrated statistically significant improvements in the PGA constipation severity, change in constipation score, and preference for treatment continuation at the end of the treatment phase, as compared to placebo in the ITT Population.

VI. Daily Symptom Scores (DSS): Change From Baseline Over the 12 Weeks:

For both Studies -00 and -03Details of the Daily Symptom Diary questionnaire are located in the Appendix. The weekly DSS is derived from the daily diary score entries reported during the Treatment Period in the patient BM and symptom diary. In both studies, plecanatide at the 3 mg dose displayed statistically significant improvements over 12 weeks compared to placebo in severity of abdominal bloating, abdominal discomfort, and abdominal pain.

Review Comments: Unlike the first four secondary endpoints reviewed above, not all of the secondary and additional endpoints are being considered for label inclusion. Both the PGA and DSS scores are not planned for inclusion in the label by the sponsor. Although the PGA score's change in constipation severity and change in constipation symptoms appear small, a statistically significant difference exists between the plecanatide intervention arms and the placebo arms. However, it is unclear in the change in these score represent clinically meaningful improvements secondary to plecanatide treatment. Similarly, the DDS score showed statistically significant differences in the plecanatide treatment versus the placebo group has not been assessed regarding the of validity of abdominal bloating, abdominal discomfort and abdominal pain. It is unclear that these changes have clinically significant meaning.

Of note, during this review process, COA requested evidence based dossiers from the sponsor in order to support the content validity of all of the secondary and additional endpoints, however the sponsor declined to provide them. Likewise, the results from the Patient Assessment of Constipation: Symptoms (PAC-SYM©) and Quality of Life (PAC-QOL©) provided additional secondary endpoints that were not evaluated in this review since the efficacy dossier was not provided by the Sponsor and these endpoints are not being considered for the labeling.

Please see the COA review regarding the validity and clinical meaningfulness of the secondary and additional endpoints.

Dose/ Dose Response: Study SP304-20210

Study SP304-20210 was a phase 2b, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, dose-ranging study in which 951 patients with CIC were randomized in a 1:1:1:1 ratio to receive an assigned plecanatide 0.3 mg, 1 mg, or 3 mg or placebo QD dosage. Patients received 12 weeks of treatment. The primary and secondary efficacy endpoints were the same the placebo-controlled phase 3 studies SP304203-00 and SP304-203-03.

Per the sponsor, this phase 2b study met its primary endpoint at the 3 mg dose, showed statistically significant improvements in secondary endpoints, in comparison to the placebo group. This finding led to the selection of the 3mg dose as one of the plecanatide doses in the phase 3 clinical studies.

The 6 mg dose usage was agreed upon with the Agency in a pre-NDA meeting in order to explore further efficacy potential of plecanatide. However, trials SP304203-00 and SP304-203-03 are not powered to detect efficacy difference between the plecanatide 3mg and 6mg treatment arms.

Durability of Response

The Applicant's primary endpoint included a requirement for patients to be a weekly responder for 3 of the last 4 weeks. This endpoint included a general assessment of durability of response. In addition, the sponsor analyzed the proportion of composite responders over weekly intervals over the 12 week period and found that the proportion of CSBMs was higher in the plecanatide treatment groups compared to placebo for each of the weeks, except for a the post-treatment weeks 13 and 14. These results support that the effects of plecanatide are durable over the course of 12 weeks of treatment. Please refer to the change from baseline in the key secondary endpoints, above.

Persistence of Effect

In Study -00, the CSBM weekly responder rate among plecanatide-treated patients compared to the placebo group was not statistically significant for either the 3 mg plecanatide group at Weeks 13 and

14 (p=0.971 and 0.707, respectively) or for the 6 mg plecanatide group at Weeks 13 and 14 (p=0.377 and 0.941). There was no evidence of any rebound worsening effect following withdrawal of plecanatide or placebo. Similar results were seen for Study -03. See the Table 31 below for results from Study -00.

Table 31: Trial SP304203-00 Post-Treatment Persistence of Effect: CSBM Weekly Responder by Week, MRA (ITT Population)

Treatment	Number (%)	
	CSBM Responders, n (%) [95% CI (%)]	Non-Responders, n (%)
Weeks 13		
Plecanatide 3mg (n=443)	76 (17.2%) [13.8, 21.0]	367 (82.8%)
Plecanatide 6 mg (n=443)	83 (19.1%) [15.5, 23.1]	351 (80.9%)
Placebo (n=448)	73 (16.3%) [13.0, 20.0]	375 (83.7%)
Weeks 14		
Plecanatide 3mg (n=443)	64 (14.4%) [11.3, 18.1]	379 (85.6%)
Plecanatide 6 mg (n=434)	57 (13.1%) [10.1, 16.7]	377 (86.9%)
Placebo (n=448)	58 (12.9%) [10.0, 16.4]	390 (87.1%)

Source: Reviewer's Table derived from Sponsor's table 14.2.2.1.1, SP304203-00

Review Comments: After the treatment phase of the trial, the discontinuation of the active medication led to a non-difference in response among all treatment arms in Study -00. This indicates that plecanatide does not have a lasting effect on CSBM or SBM beyond its expected daily treatment duration (although the half-life is not known) and that it does not create durable, long-lasting relief of constipation when it is not actively used. Study -03 showed similar results.

Additional Analyses Conducted on the Individual Trial

Pharmacokinetic Results: Study SP304203-03

From Study -03, 95 patients at nine different clinical sites participated in the PK sampling sub-study. PK samples were analyzed for 31 and 32 patients in the 3mg and 6 mg plecanatide groups, respectively; no samples were analyzed for the patients in the placebo group. Of the 63 patients with analyzed samples, 45 were females and 18 males. For all patients in the PK Population, all blood samples taken before dosing (pre-dose at Hour 0) and post-dose on Day 28 (Week 4) at 0.5, 1, 2, 3, 4, and 8 were below the limit of quantitation (BLOQ) for plecanatide and SP-338 (metabolite) concentrations.

Reviewer comment: The results from the PK substudy in study -03 indicate that plecanatide is locally acting and is minimally systemically absorbed with unmeasurable serum concentration. Please see the Clinical Pharmacology review by Dilara Jappar, PhD for further information.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoint

The efficacy results for studies SP304203-00 and SP304203-03 were pooled for analysis.

Over the 12-week treatment period, a significantly greater proportion of patients in each plecanatide treatment group were overall CSBM responders than in the placebo group for the pooled analysis. In the 3 mg plecanatide group 20.5%, (95% CI: 17.9, 23.3) of patients were overall CSBM responders compared with 11.5% (9.5, 13.8) in the placebo group (p <0.001). A similar effect was observed in the 6 mg plecanatide group, with 19.8% (17.2, 22.5) of patients categorized as overall CSBM responders (p <0.001). See Table 32 below.

Table 32: Number and Percentage of Overall CSBM Responders, MRA (ITT-E Population)

Treatment	Number (%)		
	Overall CSBM Responders, n (%)[a], [95% CI (%)[b]]	Non-Responders, n (%)	p-value
Plecanatide 3 mg (N=896)	184 (20.5%) [17.9, 23.3]	712 (79.5%)	<0.001
Plecanatide 6 mg (N=890)	176 (19.8%) [17.2, 22.5]	714 (80.2%)	<0.001
Placebo (N=897)	103 (11.5%) [9.5, 13.8]	794 (88.5%)	-

Source: Reviewer's table, adapted from Sponsor's Integrated Summary of Efficacy (ISE). Include sites 362 and 402 from Study -03.

Reviewer comment: For the primary endpoint, the results of the pooled analysis are highly statistically significant for both plecanatide treatment arms compared to placebo. As the primary endpoint required patients to be a responder for 9 of 12 weeks, including 3 of the last 4 weeks, these results indicate that plecanatide is an effective treatment of CIC with effects that are sustained over the duration of treatment. Patients with CIC may find plecanatide to be clinically meaningful in aiding to relieve their constipation by increasing the number of CSBM per week and maintaining the

relief of constipation. Of note, the study was not powered to detect statistical differences between the 3mg and the 6mg dose arm. Hence, it is unclear whether the 3mg or the 6mg dosage of plecanatide is more effective.

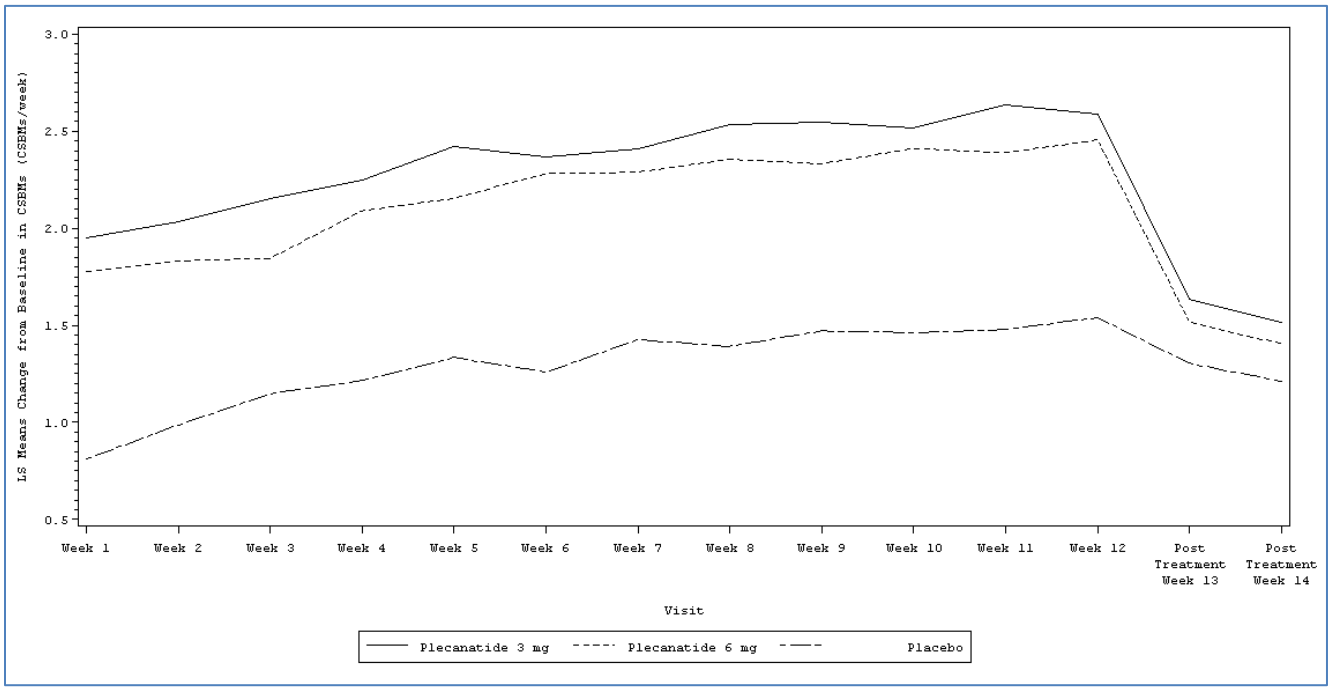
7.1.2. Secondary and Other Endpoints

CSBM Frequency

For the ITT-E population over the 12-week treatment period, each plecanatide treatment group experienced a significantly greater change from baseline in CSBM frequency compared with the placebo group. The 3 mg plecanatide group experienced a significantly greater change from baseline in CSBM frequency compared with the placebo group (difference from placebo = 1.07 [0.82, 1.33] CSBMs/week; $p < 0.001$). Similarly, the 6 mg plecanatide group experienced a significantly greater change from baseline in CSBM frequency compared with the placebo group (difference from placebo = 0.89 [0.64, 1.15] CSBMs/week; $p < 0.001$). There were no substantive differences between the plecanatide treatment groups in terms of CSBM frequency.

Weekly changes from baseline for the ITT-E population in CSBM frequency favored the 3 mg plecanatide group over the placebo group and were apparent following the first week of treatment (difference from placebo = 1.14 [0.85, 1.43] CSBMs/week; $p < 0.001$) and continuing through Week 12 (EOT; $p < 0.001$ for all time points). Similar results were noted favoring the 6 mg plecanatide group over the placebo group at each time point throughout the treatment period ($p < 0.001$ for all time points). See Figure 7 below.

Figure 7: Mean Change From Baseline in CSBMs/ Week by Time Point, MRA (ITT-E Population)



Source: Reviewer's table, adapted from Sponsor's Integrated Summary of Efficacy (ISE)
CSBM = complete spontaneous bowel movement; ITT-E = intention-to-treat efficacy; LS = least squares

7.1.3. Subpopulations

Age Subpopulations

For each endpoint analyzed using the pooled population, CSBM responders, weekly mean CSBM change from baseline, and weekly mean SBM change from baseline|, plecanatide treatment was numerically more effective than placebo in younger and older patients, both over the course of the entire treatment period and for each weekly assessment. The small population size for older patients (N = 176) likely had an effect on the analysis of this endpoint.

Table 33: Efficacy Summary Table, Age Subgroup

	3 mg Plecanatide				6 mg Plecanatide		
Durable Overall Responders							
	% (n/N)	**p-value vs placebo**			**% (n/N)**	**p-value vs placebo**	
<65 Years	20.3% (164/809)	<0.001			20.3% (163/801)	<0.001	
≥65 Years	23.0% (20/87)	0.028			14.6% (13/89)	0.440	
Change From Baseline in CSBMs (CSBMs/week[1])							
	LS mean (SE)	**Difference from placebo**	**p-value vs placebo**		**LS mean (SE)**	**Difference from placebo**	**p-value vs placebo**
<65 Years	2.35 (0.098)	1.02	<0.001		2.24 (0.098)	0.91	<0.001
≥65 Years	2.70 (0.261)	1.47	<0.001		1.92 (0.267)	0.69	0.049
Change From Baseline in SBMs (SBMs/week[2])							
	LS mean (SE)	**Difference from placebo**	**p-value vs placebo**		**LS mean (SE)**	**Difference from placebo**	**p-value vs placebo**
<65 Years	2.76 (0.136)	1.43	<0.001		2.96 (0.136)	1.63	<0.001
≥65 Years	3.67 (0.341)	2.09	<0.001		2.83 (0.349)	1.24	0.007

Source: Applicant's ISE, pg. 94; Includes sites #362 and #402. The studies were not powered for key subgroup analyses and there were no multiplicity adjustments; CSBMs = complete SBMs; LS = least squares; SBMs = spontaneous bowel movements; SE = standard error; [1] Overall average change from baseline in CSBMs across the 12-week treatment period; [2] Overall average change from baseline in SBMs across the 12-week treatment period.

Reviewer comment: The subgroup analysis by age shows that overall, that plecanatide was effective in patients over ≥ 65 years old in the integrated efficacy analysis. However, the numbers in the older age subgroup are small, and the studies were not powered for key subgroup analyses and there were no multiplicity adjustments. This reviewer feels the results from the subgroup analyses were consistent with the overall results.

Gender Subpopulations

For each primary and secondary endpoint analyzed. The 3 mg and 6 mg plecanatide treatments were generally significantly more effective than placebo for female patients, 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 (N = 358) likely had an effect on these outcomes.

Table 34: Efficacy Summary Table, Gender Subgroups

	3 mg Plecanatide				6 mg Plecanatide		
Durable Overall Responders							
	% (n/N)	**p-value vs placebo**			**% (n/N)**	**p-value vs placebo**	
Female	21.2% (151/713)	<0.001			19.6% (140/715)	<0.001	
Male	18.0% (33/183)	0.148			20.6% (36/175)	0.041	
Change From Baseline in CSBMs (CSBMs/week[1])							
	LS mean (SE)	**Difference from placebo**	**p-value vs placebo**		**LS mean (SE)**	**Difference from placebo**	**p-value vs placebo**
Female	2.44 (0.105)	1.14	<0.001		2.17 (0.105)	0.87	<0.001
Male	2.15 (0.182)	0.82	0.001		2.32 (0.186)	0.99	<0.001
Change From Baseline in SBMs (SBMs/week[2])							
	LS mean (SE)	**Difference from placebo**	**p-value vs placebo**		**LS mean (SE)**	**Difference from placebo**	**p-value vs placebo**
Female	3.21 (0.134)	1.62	<0.001		3.24 (0.134)	1.65	<0.001
Male	2.46 (0.218)	1.07	<0.001		2.72 (0.223)	1.34	<0.001

Source: pg. 106. The studies were not powered for key subgroup analyses and there were no multiplicity adjustments. Includes sites #362 and #402; CSBMs = complete SBMs; LS = least squares; SBMs = spontaneous bowel movements; SE = standard error [1] Overall average change from baseline in CSBMs across the 12-week treatment period. [2] Overall average change from baseline in SBMs across the 12-week treatment period.

Reviewer comment: The subgroup analysis by gender shows a numerically higher response rate with plecanatide than with placebo. While these results were not statistically significant in the male subgroup, the studies were not powered for key subgroup analyses and there were no multiplicity adjustments. The number of male patients were small, and it appears that overall, that plecanatide was effective in males in the integrated efficacy analysis.

Race Subpopulations

For each primary and secondary endpoint analyzed. The 3 mg and 6 mg plecanatide treatment were generally significantly more effective in white patients than placebo, both over the course of the entire treatment period and for each weekly assessment. Nonwhite patients also generally saw consistent improvements relative to placebo with both 3 mg and 6 mg doses of plecanatide.

Highly statistically significant differences were noted for the weekly mean CSBM and SBM

changes from baseline (p <0.001). The only difference seen was the lack of significance on the primary endpoint at the 6 mg dose in nonwhite patients. The small population size for nonwhite patients may have had an effect on these outcomes.

Table 35: Efficacy Summary Table, Race Subgroups

	3 mg Plecanatide			6 mg Plecanatide		
Durable Overall Responders						
	% (n/N)	**p-value vs placebo**		**% (n/N)**	**p-value vs placebo**	
White	20.1% (129/643)	<0.001		21.7% (136/626)	<0.001	
Nonwhite	21.7% (55/253)	<0.001		15.2% (40/264)	0.053	
Change From Baseline in CSBMs (CSBMs/week[1])						
	LS mean (SE)	**Difference from placebo**	**p-value vs placebo**	**LS mean (SE)**	**Difference from placebo**	**p-value vs placebo**
White	2.37 (0.116)	1.02	<0.001	2.26 (0.118)	0.92	<0.001
Nonwhite	2.35 (0.196)	1.20	<0.001	1.99 (0.190)	0.83	<0.001
Change From Baseline in SBMs (SBMs/week[2])						
	LS mean (SE)	**Difference from placebo**	**p-value vs placebo**	**LS mean (SE)**	**Difference from placebo**	**p-value vs placebo**
White	2.91 (0.148)	1.46	<0.001	3.06 (0.152)	1.61	<0.001
Nonwhite	2.79 (0.239)	1.59	<0.001	2.73 (0.232)	1.53	<0.001

Source: Applicant's ISE, pg. 119. The studies were not powered for key subgroup analyses and there were no multiplicity adjustments. Includes sites #362 and #402; CSBMs = complete SBMs; LS = least squares; SBMs = spontaneous bowel movements; SE = standard error. [1] Overall average change from baseline in CSBMs across the 12-week treatment period. [2] Overall average change from baseline in SBMs across the 12-week treatment period.

Reviewer comment: There appeared to be no difference in the response to plecanatide between white and non-white patients and both doses of the medication were equally effective.

7.1.4. Dose and Dose-Response

The recommended dose of plecanatide is a single 3 mg tablet taken once daily. The pivotal phase 3 studies confirmed the efficacy of plecanatide at the 3 mg dose using the recommended dosing paradigm and demonstrated that the 6 mg dose was significantly effective versus placebo, but not numerically superior to the 3 mg dose on most endpoints. The studies were not powered for a direct comparison of the two doses of plecanatide evaluated. As no clear efficacy benefit could be determined for the 6 mg dose, and there was a suggestion of increased

local adverse effects with this dose (see Section 8 below), only the 3 mg dose will be included in the labeling.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Plecanatide has been shown to be effective for up to 12 weeks when taken daily. For the phase 3 studies, significant differences relative to placebo were observed after the first week of treatment and maintained through the final week of treatment (Week 12). Treatment differences relative to placebo declined in subsequent post-treatment weeks and no worsening compared to baseline was noted. The regression towards baseline was greater on some endpoints than on others, but for no endpoint was there an increase in effect in the Post-Treatment Period.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-market Setting

Non-Applicable

7.2.2. Other Relevant Benefits

Reviewer comment: *The other benefits of the plecanatide for the treatment of CIC include the simple, once daily dosing schedule which is irrespective of the concomitant food and medication intake. This may make the administration and the tolerability of plecanatide beneficial to the CIC patient population.*

7.3. Integrated Assessment of Effectiveness

Reviewer comment: The submitted evidence for the effectiveness of plecanatide 3mg (b) (4) *has met the FDA evidentiary standards and supports the labeling claims for the treatment of CIC.*

The Applicant conducted two, adequate and well controlled clinical trials which independently demonstrated that plecanatide given daily for the treatment of CIC over 12 weeks, is effective in meeting its primary endpoint. The proportion of those who were primary endpoint responders was significantly greater in the plecanatide 3 mg and 6 mg treatment arms, in comparison to placebo treatment in both Studies -00 and -03. Almost twice the number of patients who took plecanatide 3mg and 6mg dosage forms, vs. placebo, were able to fulfill the primary efficacy endpoint of having at least 3 CSBMs per week and an increase of at least 1 CSBM per week above baseline in the same week. The number needed to treat (NNT) with plecanatide 3mg and 6mg in Study -00 was 9.25 and 10.7 patients, respectively; and the NNT was 13.7 and 13.9 patients in Study -03, respectively. The Sponsor's results were internally consistent across age, gender and race subpopulations. The effect of plecanatide appears early in the course of treatment, in the first week of therapy, and is generally maintained throughout the 12 week trial.

The results of secondary endpoint analyses were consistent with the primary endpoint. Specifically, the increases in the stool frequency, via the increase in number of CSBMs and SBMs in a week, may have clinical meaningfulness to many patients who suffer from CIC. Additionally, the stool consistency and straining were statistically significant and it is believed that there is clinical significance in these endpoints. The administration of plecanatide could easily fit into the treatment armamentarium for patients who suffer from CIC and provides an effective alternative option for treatment

In the label of plecanatide, the effectiveness should be presented without sites #362 and #402. The treatment difference between the two plecanatide doses and the placebo for the overall CSBM responder rated in the two phase 3 trials are presented. After taking plecanatide for 12 weeks in the phase 3 trials, patients did not suffer worsening of their constipation symptoms relative to baseline for any of the study endpoints. Since the phase 3 trials were not powered for the statistical analysis of the difference of effectiveness of plecanatide 3mg and 6mg dosages, it has not been elucidated whether one dosage is necessarily more effective than the other. Hence, this reviewer agrees with including only the 3mg dose in the label.

8 Review of Safety

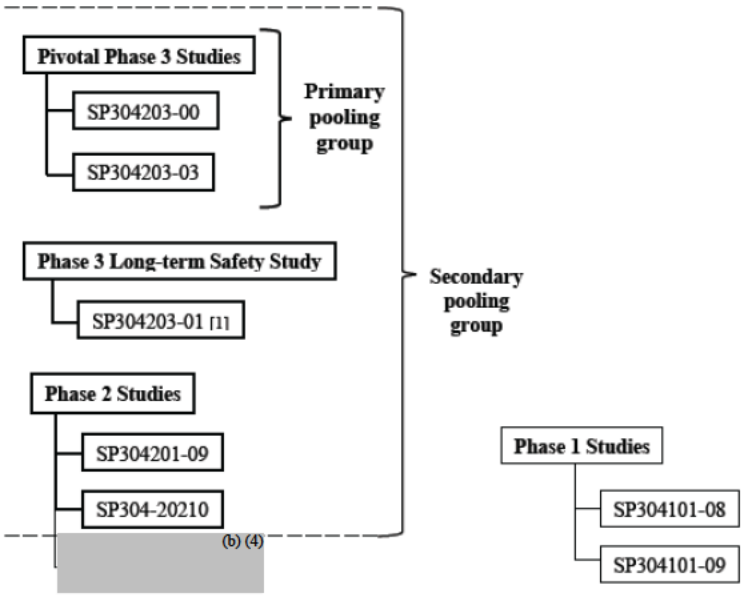
Safety Review Approach

This safety review focuses on two well-controlled, plecanatide development program phase 3 CIC studies SP304203-00 and SP304203-03. Per the sponsor, the safety population of these two studies comprise the primary safety pool. Accordingly, a secondary safety pool is comprised from the results of these two phase 3 studies and three other CIC studies in the plecanatide drug development program. Specifically, the studies that provide safety data for the secondary safety pool included the following: phase 3 studies SP304203-00 and SP304203-03 of the primary safety pool, the phase 2 trials SP304201-09 and SP30420210, and the phase 3 long-term, open-label extension study SP304203-1. (b) (4)

The primary safety pool data was used when comparing rates of common adverse events (AEs), and the secondary safety pool data was used to identify and evaluate less common, although clinically relevant safety signals throughout the entire study population. Of note, the secondary safety pool contains the data from the open-label extension study SP304203-01 ending at the time of the NDA submission. The 120-day safety update captures the remaining safety data after the completion of this study. See Table 73 in the Appendix regarding descriptions of the Phase 2 and 3 Studies that are reviewed herein.

The treatment groups included in the safety analysis includes the plecanatide 3mg QD, 6mg QD and the placebo treatment arms. All patients were analyzed according to the treatment received. During the course of the review, the Office of Scientific Integrity (OSI) determined that data from two specific sites (#362 and #402) from study SP304203-03 may pose data integrity issues due to past FDA violations. Hence, these sites were removed from select safety analysis. This issue will be discussed later in the review. Likewise, due to the integrity issues that duplicate patients pose, select safety analyses were also performed excluding duplicate patients that enrolled in more than one plecanatide study. See Figure 8 below.

Figure 8: Primary and Secondary Safety Pools Integrated Analyses



Source: Sponsor's submission, ISS pg. 31, January 29, 2016
[1] Safety results for long-term study, phase 3 study SP304203-01 include the final results from the 120 day safety update;
(b) (4)

Key Safety Review Issues Identified During Drug Development

Safety issues that were identified by the sponsor during the development of plecanatide include known safety issues associated with the CIC treatment drug class and, specifically, in the linaclotide pre- and post- marketing drug class period. Prescription products approved and being developed for CIC have been associated with diarrhea, including severe diarrhea, resulting in dehydration and electrolyte abnormalities, as well as intestinal ischemia. Concern exists for serious adverse reactions in pediatric patients stemming from juvenile mice deaths that occurred secondary to dehydration in plecanatide nonclinical studies. In addition, a theoretical concern regarding plecanatide-related immunogenicity exists regarding the potential for the creation of uroguanylin peptide depletion (UPD) syndrome.

Diarrhea: Diarrhea is expected to be one of the main adverse reactions caused by plecanatide due to the drug-class mechanism of action. In the phase 3 linaclotide studies, diarrhea was the most common adverse event seen in linaclotide-treated patients. Diarrhea and abdominal pain were the most common reasons for discontinuation of patients who were

treated with linaclotide studies.

CIC Drug Class Concerns: Moreover, a small percentage of patients reported fecal incontinence, dehydration, rectal hemorrhage, hematochezia and melena. The linaclotide clinical reviewer discussed concerns regarding the occurrences of these AEs as potential signs of ischemic colitis in their clinical review. This reviewer also evaluate the plecanatide safety data for these potential, CIC drug class concerns.

Potential Severe Dehydration in the Pediatric Age Group: There is a theoretical concern for severe dehydration in pediatric patients, particularly ≤ 2 years of age, based on the nonclinical findings of death due to severe dehydration in juvenile mice. These deaths were seen in mice ages 7d and 14 days old. The ages of these mice correlate with human pediatric ages ≤ 2 years old. Due to similar nonclinical study findings during the development of linaclotide, linaclotide is contraindicated for patients < 6 years of age. For these reasons, plecanatide potentially will be contraindicated in pediatric patients <6 years of age upon drug approval. See the nonclinical review by Dr. Eddie NG for further details.

Potential Uroguanylin Peptide Depletion (UPD) Syndrome: In the review of linaclotide, due to the structural homology to endogenous guanylin peptide family members, there existed a theoretical concern for the development of uroguanylin peptide deficiency if anti-linaclotide antibodies were to develop and cross-react with endogenous peptides. As plecanatide also has structural homology to endogenous guanylin peptide, this theoretical concern for AEs associated with UPD syndrome also exists for plecanatide. Signals of adverse events potentially related to this deficiency (i.e., AEs suggestive of fluid/volume overload) syndrome state were explored, including congestive heart failure (CHF), dyspnea, exertional dyspnea, pulmonary congestion, pulmonary, edema, peripheral edema, weight increase, blood pressure increase, hypertension, fluid retention, and hypernatremia, pancreatitis and pancreatic insufficiency.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety analysis data set were defined as all enrolled patients who received at least one dose of study drug. Any analysis based on the safety analysis set was based on the treatments actually received. Data include duplicate patients who were identified as having participated in one or more study site or in another plecanatide study. Therefore, duplicate patients may appear more than once in the safety populations of studies SP304203-00, SP304203-03, SP304203-01, SP304-20210, (b) (4) thus, instances of duplicate participation by the same patient were analyzed as discreet participants in the primary and secondary pooled safety population. In addition, there are patients identified as receiving incorrect study drug kits and may have taken more than one study drug dose level of during the course of the study period. These patients were analyzed according to the maximum dose of study drug received at any time during study treatment, regardless of the number of treatment experiences (unique patient identifiers). Data was analyzed according to the actual treatment that the patient received.

See the tables below for the number of patients exposed to all doses of plecanatide and, specifically, to 3mg and 6mg doses throughout the plecanatide development program.

Table 36: Patients Exposed to All Plecanatide Doses and Duration (Months)

Number of patients exposed to plecanatide (any dose):			
Any exposure	>=3 months	>= 6 months	>= 12 months
N=3833	N=1389	N=890	N=599

Source: Sponsor's IR response September 26, 2016; Excluding duplicate patients; Exposure to all doses in the plecanatide program studies.

Table 37: Patients Exposed to Plecanatide Doses and Duration (Days)

	Duration of Exposure to any dose of plecanatide (Days)	Duration of Exposure to plecanatide 3 or 6 mg (Days)
N	3833	3454
Mean	149.7	155.9
SD	155.78	156.86
Median	85.0	85.0
Minimum	1	1
Maximum	718	718

Source: Sponsor's IR response September 26, 2016; Excluding duplicate patients. SD = standard deviation. Duration of exposure = date of last dose of study drug - date of first dose of study drug + 1. The last dose date for patients lost to follow-up was the last date of contact, which accounts for exposure beyond protocol-allowed visit windows.

Table 38: Patients Exposed to Plecanatide 3mg and 6mg Doses and Duration (Months)

Number of patients exposed to plecanatide 3mg or 6mg			
Any exposure	>=3 months	>= 6 months	>= 12 months
N=3454	N=1357	N=886	N=595

Source: Sponsor's IR response September 26, 2016; Excluding duplicate patients; Exposure to 3mg and 6mg doses in the plecanatide program studies

Reviewer comment: The patient exposure to plecanatide in the development program meets the minimum specified numbers of patients in the ICH guideline recommendation. The number of patients with a cumulative duration of exposure of 12 months or longer exceed the respective agreed-upon number at the pre-NDA meeting on August 5, 2015, which were 159 patients for 3 mg plecanatide and 325 patients for 6 mg plecanatide.

Table 39: Duration of Plecanatide Exposures by Days – All Doses and 3mg and 6mg

	Duration of Exposure to any dose of plecanatide (Days)	Duration of Exposure to plecanatide 3 or 6 mg (Days)
N	3833	3454
Mean	149.7	155.9
SD	155.78	156.86
Median	85.0	85.0
Minimum	1	1
Maximum	718	718

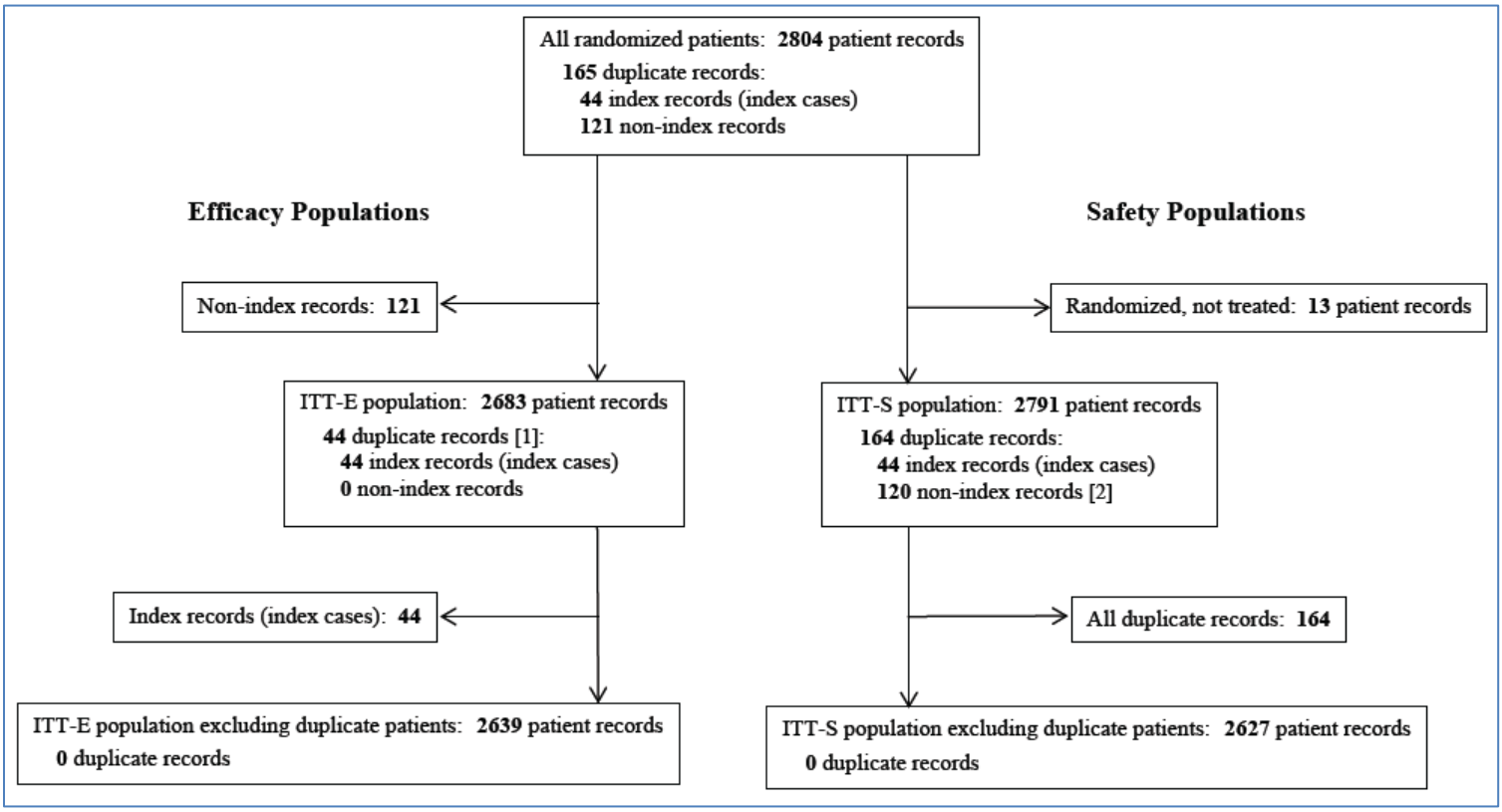
Source: Sponsor's IR response September 26, 2016; Excluding duplicate patients. SD = standard deviation. Duration of exposure = date of last dose of study drug - date of first dose of study drug + 1. The last dose date for patients lost to follow-up was the last date of contact, which accounts for exposure beyond protocol-allowed visit windows.

Primary Safety Pool - Duplicate Patients

The primary safety pool, including duplicate patients and sites #362 and #402 of study SP304203-03, is composed of 2791 patients from the controlled phase 3 studies, including: 924 in the placebo group, 941 in the 3 mg plecanatide group, and 926 in the 6 mg plecanatide group. One hundred sixty-four (5.9%) of the total 2791 patients in the primary pool, were considered duplicate patients, meaning they had more than one patient record included in the safety analyses. With the exclusion of duplicate patients, there were 2627 patient records included in the primary safety pool.

For more details, see Figure 9 below regarding the handling of duplicated patients in the safety populations in contrast with the efficacy populations. Please note that the sponsor's figure uses the terms ITT-S and ITT-E to refer to the safety and efficacy analysis populations; however, this reviewer will use the terms primary and secondary safety pools to refer to the safety analysis populations in this review.

Figure 9: Disposition of Duplicated Patients in the Primary Safety Pool



Source: Sponsor's submission, ISS pg. 33, January 29, 2016. Includes sites #362 and #402; ISE = Integrated Summary of Effectiveness; ISS = Integrated Summary of Safety; ITT-E = intention-to-treat efficacy; ITT-S = intention-to-treat safety; [1] Non-index duplicate patients were removed from the ITT-E population. [2] One duplicate patient was not dosed and therefore the ITT-S population has 1 less duplicate patient.

Primary and Secondary Safety Pools Total Patients

Table 40 shows the overall number of patients that comprise each study of the primary and secondary safety pools. These numbers include duplicate patients, sites #362 and #402 and patients are counted twice if re-enrolled in the open-label, long-term safety study SP304203-01.

Table 40: Plecanatide Safety Populations Studies and Treatment Group

Clinical Trial Groups	Description of Study Type	Plecanatide 3mg	Plecanatide 6mg	Placebo	Total Patients
Primary Pool Safety Population					
SP304203-00	R,DB,PC, Phase 3	474	457	458	1389
SP304203-03	R, DB,PC, Phase 3	467	469	466	1402
Additional Studies Comprising Secondary Safety Pool Population					
SP304203-01*	Long-term, open-label extension, Phase 3	224	2146	N/A	2370
SP304201-09	R, DB,PC, Phase 2	15	N/A	20	35
SP30420210	R, DB,PC, Phase 2	237	N/A	236	473

Source: Reviewer's table, adapted from Sponsor's Application 120 day safety report May 27, 2016; Including duplicates and sites #362 and #402, R= randomized, DB= double-blinded, PC= placebo-controlled; Note: *Patients are summarized under each treatment level dosed across all studies in the pool and therefore may appear under a treatment column more than once. Analysis does not account for interruptions between each episode of exposure.

Reviewer comment: The sponsor adequately created the safety populations by categorized patients in the arms based on the actual medication received. This method of analysis of the patients per the actual drug dose or placebo received is equivalent to an "as treated" population. The pooling of data as presented by the applicant is acceptable, as patients from these studies are believed to be sufficiently similar.

Duplicates only comprised 5.9 % (n=164) of the safety population in the primary safety pool. Of these, only 4.3% were non-index records (n=120). Although this reviewer agrees with the use of the duplicated patient case in the primary and secondary pooled safety analysis, for

better clarity and data integrity concerns, specific data analysis is presented in this safety review that does not include the duplicated patients nor patients from sites #362 and #402 of study SP304203-03.

Explorations for Dose Response

The doses of plecanatide selected for the SP304203-00 and -03, phase 3 studies were based primarily on the phase 2 CIC dose-ranging studies. The sponsor explored a total of four doses, 0.3mg, 1mg, 3mg, and 9mg, compared with a placebo group in their phase 2 studies SP304201-09 and SP304-20210.

Study SP304-20201-09 was a 14-day repeat-dose, placebo-controlled, dose-ranging PK/PD and safety study in which 0.3, 1.0, 3.0, and 9.0 mg QD plecanatide were assessed. In this study, patients in the 9.0 mg plecanatide group did not report more GI side effects, as compared with patient in the 0.3mg, 1mg, or 3mg dose groups. Study SP304020210 was a dose-ranging study which evaluated 0.3 mg QD, 1 mg QD, and 3 mg QD of plecanatide over a 12 week time period. In this study, the plecanatide 3 mg dose showed the greatest treatment effect with statistical significance on the primary and secondary endpoints.

In the SP304-20210 study, the incidence of diarrhea showed a positive relationship to increasing dose levels, but diarrhea only increased from 8.4% at the 1.0 mg plecanatide dose to 9.7% at the 3.0 mg plecanatide dose. Per the sponsor, the linear increase in efficacy and nonlinear increase in the incidence of diarrhea were favorable for testing a higher dose of plecanatide to evaluate if even higher overall response rates can be achieved without incrementally increasing the incidence of diarrhea, or otherwise adversely affecting the tolerability profile of plecanatide. Hence, the plecanatide 6 mg dose was tested in the phase 3 studies for this reason. See Table 41 below for the common AEs reported in study SP304-20210.

Table 41: Phase 2B Study SP304-20210: AEs in Patients ≥ 2% in the Plecanatide Treatment Groups

Adverse Events (PT)	Placebo N= 236	Plecanatide 0.3 mg N= 237	Plecanatide 1 mg N= 238	Plecanatide 3mg N= 237	Total patients with the AEs N= 948 n (%)
Diarrhea	3 (1.3%)	13 (5.5%)	20 (8.4%)	23 (9.7%)	59 (3.4%)
Flatulence	5 (2.1%)	5 (2.1%)	3 (1.3%)	14 (5.9%)	27 (1.6%)
Abdominal pain	11 (4.7%)	6 (2.5%)	10 (4.2%)	12 (5.1%)	39 (2.3%)
Abdominal distension	5 (2.1%)	5 (2.1%)	10 (4.2%)	9 (3.8%)	29 (1.7%)
Headache	5 (2.1%)	10 (4.2%)	11 (4.6%)	9 (3.8%)	35 (2.0%)
Upper respiratory tract infection	5 (2.1%)	6 (2.5%)	5 (2.1%)	9 (3.8%)	25 (1.5%)
Nausea	5 (2.1%)	5 (2.1%)	12 (5.0%)	8 (3.4%)	30 (1.7%)
Urinary tract infection	6 (2.5%)	5 (2.1%)	9 (3.8%)	8 (3.4%)	28 (1.6%)
Abdominal tenderness	1 (0.4%)	2 (0.8%)	0	4 (1.7%)	7 (0.4%)
Nasopharyngitis	5 (2.1%)	5 (2.1%)	3 (1.3%)	4 (1.7%)	17 (1.0%)

Source: Reviewer's analysis, JReview 9.2; derived from ISS Analysis dataset Adam: ADAE and ADSL

Reviewer comment: Diarrhea was the most common AE in patients treated with plecanatide in the SP304-20210 phase 2B study, in comparison to the placebo group. This made diarrhea an AE of specific concern for the phase 3 studies. No other AEs, except for possibly flatulence, were more common in the plecanatide treatment group versus the placebo group in this study.

When looking at the data of the secondary pooled studies, the adverse event rates were similar between dosing groups. There were more SAEs and AEs leading to discontinuation in the plecanatide treatment groups in comparison to placebo. See Table 42 below for an

overview of the types of AEs in all dose groups of the studies that comprise the secondary safety pool.

Table 42: Overview of AE Types in the Secondary Safety Pool All Dose groups

Overall N=5594	Placebo N=1180 n (%)	Plecanatide 0.3 mg N= 251 n (%)	Plecanatide 1 mg N= 252 n (%)	Plecanatide 3 mg N= 1403 n (%)	Plecanatide 6 mg N= 2118 n (%)	Plecanatide 9 mg N= 15 n (%)
Adverse Events	365 (31%)	102 (41%)	122 (48%)	519 (37%)	779 (31%)	6 (40%)
Serious Adverse Events	18 (1.5%)	1 (0.4%)	1 (0.4%)	24 (1.7%)	31 (1.3%)	0
Adverse Events Leading to Discontinuation	30 (2.5%)	10 (4.0%)	16 (6.3%)	66 (4.7%)	141 (5.7%)	0

Source: Adapted from Sponsor's ISS Table 18; Includes duplicate patients and sites #362 and #402. Note: Patients were summarized under every occurrence of an event at each treatment level across all studies in the pool and therefore may appear under a treatment column more than once.

Reviewer comment: The justification for the plecanatide doses of 3mg and 6mg QD appear reasonable, given the results of the phase 2 dose-ranging studies. It is reassuring that doses that were both lower 3mg and higher than 6mg were considered and evaluated in these studies. Although the 6mg dose was not evaluated until the phase 3 trials, in the phase 2 trials, the 3 mg appeared to have greater efficacy than other doses, and a separate study assessing a 9.0 mg dose was not associated with additional GI side effects. In order to determine if any additional benefit could be gained with the higher dose, the applicant's strategy to test a second dose higher than 3 mg during the phase 3 studies was reasonable. Please see the Clinical Pharmacologist Dr. Dilara Jappar review for additional details.

8.2.2. Relevant Characteristics of the Safety Population

Demographics

The majority of patients in the primary pool, excluding patients from sites #362 and #402, were female (79%) and less than 65 years of age (90%). The overall median (min, max) age was 46.0 (18, 80) years. The predominant race was white/Caucasian (71%), followed by black or African American (24%). Over half of all patients (58.3%) were non-Hispanic. The median BMI was

27.7kg/m^2, and patients were generally evenly distributed across BMI categories of underweight to normal (28%), overweight (39%), and obese (33%). Demographic and baseline characteristics were similar across the placebo, 3 mg plecanatide, and 6 mg plecanatide groups. The demographics in the secondary safety pool were similar to those of the primary pool.

Concomitant Medications

A total of 1935 patients (69.3%) in the primary safety pool reported use of at least 1 concomitant medication. The most frequently reported drug classes of concomitant medications were propionic acid derivatives (14.0%), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) inhibitors (11.1%), proton pump inhibitors (10.6%), multivitamins/other combinations (10.0%), angiotensin-converting enzyme inhibitors (8.7%), platelet aggregation inhibitors excluding heparin (8.0%), selective serotonin reuptake inhibitors (7.2%), vitamin D and analogs (7.2%), anilides (7.0%), thyroid hormones (6.9%), biguanides (5.9%), other antidepressants (5.9%), benzodiazepine derivatives (5.7%), progestogens and estrogens/fixed combinations (5.4%), and other combinations of nutrients (5.1%). The percentages of patients using each of these classes of concomitant medication were similar across the placebo, 3 mg plecanatide, and 6 mg plecanatide groups. This finding also generally applied to other drug classes reported by at least 2% of patients overall.

Reviewer comment: The safety database appears adequate and includes a population that is sufficiently diverse to represent the target population that suffers from CIC. This development program appears to have sufficient safety data in a broad population that can allow for generalizability of the safety findings. Plecanatide is not expected to have a drug-drug interaction with the concomitant medication since plecanatide is believed to be minimally absorbed. When omitting duplicate patients and sites #362 and #402 of study SP304203-03 from the demographic analysis, there is minimal change in the percentages and the no important differences exist in the proportions of patients in the various demographic groups among the treatment groups in the primary and secondary safety pools.

8.2.3. Adequacy of the Safety Database

Reviewer comment: As commented above, the safety database for plecanatide is comprehensive and adequate to assess safety of this drug for the proposed indication, dosage regimen, duration

of treatment and the patient population. The submission quality is adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the submission was adequate to perform the safety review for plecanatide. The Office of Computational Science (OCS) performed the Jump Start service data fitness analysis and found no major issues that would preclude performing a safety review.

However, upon review of the safety database, there were a few concerns regarding data integrity that had an effect on the safety review, including the data unlocking and relocking as described in section 6. The OSI consult determined two sites that had questionable data integrity issues that were identified from FDA enforcement actions in previous studies were removed in subsequent analysis of the efficacy and safety data. These removed sites, #362 and 402, were from study SP304203-03 and comprised 30 patients total: Placebo group (n=6); Plecanatide 3mg group (n=14) and 6mg group (n=10). Please see the consult from OSI Dr. Susan Leibenhaut.

Additionally, there were 164 duplicate patients that were randomized more than one time in the primary safety pool studies. Of these, 44 randomizations of these duplicate patients were considered to the patient's first time enrollment and are identified as index patients. Duplicate patients, except for the index cases, were also removed from select safety analysis performed in this review.

In regards to immunogenicity, the sponsor did not provide adequate data results from the immunogenicity samples, since the anti-drug antibody (ADA) assays were not completely developed. The sponsor communicated that they expected to have screening and confirmatory immunogenicity assays and accompanying data by the 120-safety update during this review. However, appropriate ADA assay information were not submitted at that time and remain outstanding at the time of this review.

<u>Reviewer comment:</u> Overall, the data appears to have good integrity based on my evaluation, and the evaluation from OSI and OCS offices. The safety analysis from this data should be

dependable and lead to an accurate assessment of the safety of plecanatide. The removal of the two sites with potential data integrity issues and duplicate patients should not have a great impact of the safety results in the study. In regards to immunogenicity, although it is believed the plecanatide has minimal absorption and was not detected in human pharmacokinetic studies, the sponsor will be required to develop adequate assays to assess anti-plecanatide antibodies.

8.3.2. Categorization of Adverse Events (AEs)

There were no identified issues with respect to recording, coding, and categorizing AEs. The sponsor categorized serious adverse events (SAEs) in accordance with standard, regulatory definitions. The Medical Dictionary for Regulatory Activities (MedDRa) version 14.1 was used in the safety analysis and the sponsor analyzed all of the AE terms at both the primary and secondary SOC levels, by using Standard MedDRA Queries (SMQs). Severity of AEs was classified by the National Cancer Institute-Common Terminology Criteria for Adverse events (CTCAE) v4.03.

An AE was classified as any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related. An AE was any unfavorable and unintended sign - including abnormal laboratory finding - symptom, or disease temporally associated with the use of plecanatide or the placebo. Concomitant illnesses, which existed before entry into the study, was not considered AEs unless they worsen during the treatment period.

A Treatment Emergent Adverse event (TEAE) was defined as an AE that begins or that worsens in frequency and/or severity after at least one dose of study drug has been administered. The sponsor states that even minor fluctuations in laboratory values for standard monitoring (abnormal values) that an investigator did not consider clinically significant or related to study drug was recorded as AEs. However, if the laboratory abnormality is associated with a diagnosis, then the AE term for that diagnosis was reported.

Since an increase in the number of BMs from baseline was an expected pharmacodynamic effect of plecanatide and would be coded as diarrhea, sites were instructed to only record an AE of diarrhea if the patient reports that it was bothersome [e.g., watery / mushy stool (BSFS score of 6 or 7), with a sense of urgency, etc.] or if the event required treatment or hospitalization.

Reporting AEs

Adverse event reporting extended from the patient signing the informed consent form until the completion of the final visit that was considered to be the End of the Post-Treatment Period. Adverse events occurring after the end of the study were reported to the sponsor by investigators if an investigator considers there to be a causal relationship to the study drug.

All AE reports were requested to contain a brief description of the event, date of onset, date of resolution, intensity, treatment required, the relationship to study drug, action taken with the study drug, outcome of the adverse event, and whether the event is classified as serious. The adverse events were assessed by the frequency of events per patient. All AEs experienced by patients who are randomized to treatment, regardless of the relationship to study drug, were reported. For patients who were screen failures, only serious adverse events (SAEs) were reported.

Serious Adverse Events (SAEs)

A SAE was defined as an untoward medical occurrence, at any study-drug dose, and included one of the following:

1. Resulted in death
2. Was life-threatening (an adverse event or suspected adverse reaction was considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence placed the patient at immediate risk of death. It did not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
3. Required inpatient hospitalization or prolongation of existing hospitalization
4. Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Was a congenital anomaly or birth defect (in a patient offspring)
6. Was a medically important event (examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization or the development of drug dependency or drug abuse)

Additional *"Medically Important Events"* were reported as SAEs, including cases of elevated hepatic enzyme levels:

1. Aminotransferases (ALT or AST) are > 3 times the upper limit of normal (ULN) with an associated elevation of Total Bilirubin > 2 times ULN without evidence of hemolysis or with alkaline phosphatase < 2 times ULN (or not available)
2. Or, ALT or AST activity that is > 5 times the ULN

Of note, pregnancy events were also reported on the SAE record forms during the plecanatide drug development program even though they were considered to be "true" SAEs.

Reporting SAEs

All SAEs that occur during the study, as defined by the protocol, were required to be reported by the investigator to a designated safety contact within 24 hours from the point in time when the investigator/site became aware of the SAE. In addition, all SAEs including any deaths, which occur up to and including 30 days after the administration of the last dose of the study medication, was required to be reported. All SAEs and deaths were required to be reported whether or not considered causally related to the study medication, including any SAE that occurred at any time after completion of the study (i.e., beyond 30 days after last study drug dose).

Severity

The severity levels of the AEs were assessed according to the following general categorical descriptors:

- *Mild:* asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- *Moderate:* minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
- *Severe*: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL include bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)

Of note, AEs labeled as having severe intensity were not necessarily considered to be SAEs. Accordingly, AEs of mild severity AE (such as a mild stroke) could have been considered as an SAE (see below).

Causality

The causal relationship of the AE to study drug was described in terms of:

- *Reasonable Possibility:* There was evidence to suggest a causal relationship between the drug and the AE (e.g., AE is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure)
- *No Reasonable Possibility:* This categorization was used if there was no evidence to suggest a causal relationship between the drug and the AE. The most likely cause of an AE or SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) was indicated with details of the concomitant disease or medication or other cause.

Adverse Events Follow-up

All AEs experienced by a patient, irrespective of the suspected causality, was monitored until the AE resolved, or any abnormal laboratory values returned to baseline, or stabilized at a level acceptable to the investigator and the medical monitor.

Pregnancy

Efforts were made to avoid pregnancy in this study. However, if a female patient became pregnant during the study, the investigator was required to notify the sponsor upon becoming aware of the pregnancy. Pregnancy itself was not considered to be true AEs or SAEs, however pregnancies were tracked and reported in the safety (SAE) database are were listed as SAEs. Pregnant patients were immediately discontinued from the study but will be followed for the duration of the pregnancy. Details of the outcome of the pregnancy (e.g., full term normal delivery, stillbirth, congenital anomalies, and miscarriage) were attempted to be collected and reported by the site.

All reports of congenital abnormalities/birth defects of patient offspring were SAEs. Spontaneous miscarriages were also reported and handled as SAEs. However, elective abortions without complications were not handled as SAEs.

Reviewer comment: The categorization of adverse events were overall adequate and reasonable. The sponsor appropriately used a modern version of the MedDRA coding system for AEs and grading scale to assess severity.

However, this reviewer noticed that in the reporting of abdominal pain, an AE of interest, that there was "splitting" of this symptom into multiple preferred terms (PTs): abdominal pain, abdominal pain upper and abdominal pain lower. These AEs were subsequently analyzed with other abdominal pain related AEs, including abdominal distention, abdominal discomfort and abdominal tenderness. This is described in Section 8.5 Analysis of Submission-Specific Safety Issues below.

8.3.3. **Routine Clinical Tests**

Routine laboratory tests (hematology, serum chemistry, and urinalysis) in the primary pool were collected at screening, Weeks 1, 4, 8, and 12 (end of treatment), and end of study or early withdrawal. A six to twelve hour fast was recommended for laboratory tests. Follicle-stimulating hormone and thyroid-stimulating hormone levels were assessed only at screening. Blood samples for immunogenicity testing for antibodies to plecanatide were collected and banked at pre-dose hour 0 (Week 1, Day 1 Treatment Period Visit), Weeks 4 (or at Week 8 if trough sample were not collected prior to the patients' morning dose at Week 4), and at EOS or at early withdrawal (EW).

Grades for laboratory results were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

The timing of the other safety tests, including pharmacokinetic testing, pregnancy tests and drug screen is presented in the Schedule of Assessments in the Appendix. The laboratory variables presented in the Table 43 below were assessed in accordance with the Schedule of Assessments in studies SP30203-00 and -03.

Table 43: Laboratory Assessments for Studies SP30203-00 and -03

Hematology:	Erythrocytes, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin, and hematocrit
Urinalysis:	Specific gravity, pH, protein, glucose, ketones, blood, and microscopic examination of sediment
Serum chemistry:	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, total bilirubin, direct bilirubin, blood urea nitrogen, total protein, albumin, uric acid, glucose, amylase, lipase, triglycerides, and cholesterol.
Hormone:	FSH, TSH (T_3 and free T_4 if TSH is out of range) at screening only to help determine eligibility.
Electrolytes:	Sodium, potassium, chloride, magnesium, phosphorus, calcium
Pregnancy test:	Urine pregnancy tests at the Screening Visit and at Day 1 (Week 1), Week 12 (EOT) and Week 14 (EOS) Visits
Urine Screen for Substances of Abuse	Opioids including methadone, morphine, and oxycodone. Urine drugs of abuse screen will be conducted at Screening and on Day 1.

Source: Sponsor's Protocol SP304203-00 and -03

Vital Signs

Vital sign measurements included heart rate, diastolic and systolic blood pressure, respiratory rate, temperature, and weight. These were assessed in accordance with the study's Schedule of Assessments. In the primary pool, assessment of vital signs were performed at Screening; Weeks 1, 4, 8, and 12 (end of treatment); and end of study or early withdrawal. Blood pressure (systolic and diastolic; mmHg), heart rate (beats per minute), body temperature (°C), respiration rate (breaths per minute), and weight (kg) were measured at all visits with the same calibrated scale and same conditions (shoes off) used for each measurement. Measurements were performed after the patient was seated for at least 5 minutes.

EKG

Standard 12-lead ECGs was performed in accordance with the Schedule of Assessments. All ECGs were performed in the semi-recumbent position. A standard, 12-lead ECG was performed at approximately one-hour post-dose on Day 1 (with a +/- 30-minute window). A standard 12-

lead ECG was also done at Week 12 or the Early Termination Visit. ECGs performed in studies SP304203-00 and SP304203-03 were interpreted by a qualified evaluator at the study center. The studies did not conduct a central evaluation of ECGs. Clinically significant ECG findings, as determined by the investigator, were reported as AEs.

Physical Examinations

Physical examinations (PEs) were performed in accordance with the Schedule of Assessments and included an assessment of general appearance, head (ear, eyes, nose, and throat), cardiovascular, respiratory system, abdomen, musculoskeletal, neurological, lymph nodes, and skin. Height was measured at the Screening Visit only. Weight was measured as part of all PEs, with the same calibrated scale used for each measurement. At the screening visit only, the PE also included a digital rectal examination (DRE) to check for blood in the stool and anatomical abnormalities. A positive occult blood reading did not exclude the patient as patients with hemorrhoids could be entered into the study. If blood was found in the stool, a colonoscopy may have been required, at the discretion of the Investigator, to ensure there are no exclusionary underlying conditions.

Reviewer comment: The safety of plecanatide was assessed throughout the clinical development program through the monitoring of AEs, 12-lead ECGs, physical exam findings, vital sign measurements, clinical laboratory assessments, concomitant medications, and pregnancy tests for women. These safety assessments were reasonable for the intended population of patients with CIC.

8.4. Safety Results

Death

One death occurred in the CIC clinical development program for plecanatide, which was reported in the ISS. This death is not attributed to the study drug. The narrative of this report is included below.

Patient 630-105: Myocardial Infarction: plecanatide 6mg QD, SP304203-01

This patient was a 47-year-old male who began treatment with 6 mg plecanatide in June 2014. After 2 years of reported abstinence from substance abuse, he used crack cocaine, intravenous heroin, and alcohol soon after the initiation of the study. (b) (6) months after starting plecanatide, the patient was hospitalized with acute renal insufficiency (creatinine 2 mg/dL) and myocardial infarction. The myocardial infarction was attributed to recent cocaine abuse in the setting of underlying coronary disease, and the event was considered resolved at the time of discharge. Likewise, the event of acute renal failure was considered resolved by the same day with sequelae (creatinine 1.1 mg/dL). Less than a month after discharge, the patient experienced another myocardial infarction at home, which was fatal. The investigator reported that the autopsy report was not available. Both the first and second events of myocardial infarction and the event of acute renal failure were not considered to be related to the study drug.

Reviewer comment: Myocardial infarction related deaths are not uncommon in patients who abuse illicit drugs such as cocaine. Due to the patient's illicit drug use and underlying coronary disease, his myocardial infarction death most likely was due to the use of illicit drugs and not to plecanatide.

8.4.2. Non-fatal Serious Adverse Events (SAEs)

Overview of Adverse Events (AEs) in the Primary Safety Pool

In the primary safety pool, there were fairly equal proportions of patients who reported any AE or serious AEs in plecanatide treatment groups versus the placebo group; and none led to death. Table 44 below is an overview of the types of AEs in the controlled phase 3 studies.

Table 44: Overview of AEs in Primary Safety Pool

Adverse Events (AEs) N=2601 n, %	Treatment Weeks 1-12					
	Plecanatide 3mg (N=863)		Plecanatide 6 mg (N=868)		Placebo (N=870)	
Patients with any AEs	274	31.7%	282	32.5%	255	29.3%
Possible Relatedness to the Study Drug (Causality)	82	9.5%	89	10.3%	43	4.9%
Patients with Severe AEs	20	2.3%	23	2.6%	13	1.5%
Patients with any Serious AEs (SAEs)	13	1.5%	9	1.0%	11	1.3%
Patients with any AEs leading to death	0	0	0	0	0	0
Patients with any AEs leading to permanent treatment discontinuation	38	4.4%	42	4.8%	20	2.3%

Source: Reviewer's Table, derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2
Excluding duplicate patients and sites #362 and #402 from study SP304203-03

Overview of SAEs in the Primary Safety Pool

During Studies SP304203-00 and SP304203-03, a total of 33 patients (1.3%) reported SAEs. The incidence was similar in the plecanatide 3 mg, plecanatide 6 mg and placebo groups (1.5%, 1.0%, and 1.3%, respectively). Accordingly, the most frequently reported system organ class (SOC) of SAEs in the plecanatide arms was investigations (0.3%) which included abnormal hepatic enzymes. See Table 45, which includes duplicate patients and those from sites #362 and #402 from study SP304203-03 below for the types of SAEs in the primary safety pool.

Table 45: Primary Safety Pool SAEs per SOC and PT

System Organ Class Preferred Term	Placebo (N = 924) n (%) E	Plecanatide			Overall (N = 2791) n (%) E
		3 mg (N = 941) n (%) E	6 mg (N = 926) n (%) E	Combined (N = 1867) n (%) E	
Number of patients with SAEs and number of events	12 (1.3) 13	14 (1.5) 15	9 (1.0) 9	23 (1.2) 24	35 (1.3) 37
Gastrointestinal disorders	0	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2	2 (0.1) 2
Intestinal obstruction	0	1 (0.1) 1	0	1 (0.1) 1	1 (0.0) 1
Pancreatitis acute	0	0	1 (0.1) 1	1 (0.1) 1	1 (0.0) 1
Hepatobiliary disorders	0	2 (0.2) 2	0	2 (0.1) 2	2 (0.1) 2
Cholecystitis	0	1 (0.1) 1	0	1 (0.1) 1	1 (0.0) 1
Cholelithiasis	0	1 (0.1) 1	0	1 (0.1) 1	1 (0.0) 1
Infections and infestations	3 (0.3) 3	0	2 (0.2) 2	2 (0.1) 2	5 (0.2) 5
Diverticulitis	1 (0.1) 1	0	0	0	1 (0.0) 1
Gastroenteritis	0	0	1 (0.1) 1	1 (0.1) 1	1 (0.0) 1
Mastitis	1 (0.1) 1	0	0	0	1 (0.0) 1
Pneumonia	1 (0.1) 1	0	0	0	1 (0.0) 1
Staphylococcal infection	0	0	1 (0.1) 1	1 (0.1) 1	1 (0.0) 1
Injury, poisoning and procedural complications	1 (0.1) 1	0	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Ankle fracture	0	0	1 (0.1) 1	1 (0.1) 1	1 (0.0) 1
Femoral neck fracture	1 (0.1) 1	0	0	0	1 (0.0) 1
Investigations	1 (0.1) 1	4 (0.4) 4	1 (0.1) 1	5 (0.3) 5	6 (0.2) 6
Alanine aminotransferase increased	1 (0.1) 1	1 (0.1) 1	0	1 (0.1) 1	2 (0.1) 2
Aspartate aminotransferase	0	2 (0.2) 2	0	2 (0.1) 2	2 (0.1) 2
Liver function test abnormal	0	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2	2 (0.1) 2
Nervous system disorders	0	1 (0.1) 1	2 (0.2) 2	3 (0.2) 3	3 (0.1) 3
Cerebral infarction	0	1 (0.1) 1	0	1 (0.1) 1	1 (0.0) 1
Convulsion	0	0	1 (0.1) 1	1 (0.1) 1	1 (0.0) 1
Headache	0	0	1 (0.1) 1	1 (0.1) 1	1 (0.0) 1
Pregnancy and perinatal	2 (0.2) 3	3 (0.3) 3	1 (0.1) 1	4 (0.2) 4	6 (0.2) 7
Abortion spontaneous	1 (0.1) 1	0	0	0	1 (0.0) 1
Pregnancy	2 (0.2) 2	3 (0.3) 3	1 (0.1) 1	4 (0.2) 4	6 (0.2) 6
Respiratory, thoracic and mediastinal disorders	0	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2	2 (0.1) 2
Chronic obstructive pulmonary	0	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2	2 (0.1) 2
Vascular disorders	2 (0.2) 2	0	0	0	2 (0.1) 2
Arterial occlusive disease	1 (0.1) 1	0	0	0	1 (0.0) 1
Peripheral arterial occlusive disease	1 (0.1) 1	0	0	0	1 (0.0) 1

Source: Sponsor's Table 31, ISS. Post-text Table 14.3.1.3.1.1.1, Includes duplicates and sites #362 and #402 from study SP304203-03.

Reviewer comment: *The overall rates of serious adverse events in the primary pool were fairly low and the proportions were similar across treatment arms. When duplicate patients and those from sites #362 and #402 are removed, two SAEs are removed. Of note, there were no SAEs of diarrhea or diarrhea-related sequelae. These represent favorable results for both doses of plecanatide. Select cases of elevated hepatic enzymes and other SAEs are discussed in detail later in this review.*

Overview of SAEs in the Secondary Safety Pool

Based on the sponsor's 120-day safety update submission, a total of 83 patients (1.5%) reported 99 SAEs in the Secondary Safety Pool. Within these SOCs, the most frequently reported PT of SAEs in the plecanatide groups (excluding pregnancy) were the following: non-cardiac chest pain, elevated ALT, AST, and LFTs that include alanine aminotransferase increased (n=3) and aspartate aminotransferase increased/abnormal (n=4). In addition, cholecystitis was reported in 3 patients. Other SAEs reported in plecanatide patients each were atrial fibrillation, congestive cardiac failure, gastroesophageal reflux disease, cholelithiasis, diverticulitis, gastroenteritis, ankle fracture, liver function test abnormal, spontaneous abortion, and chronic obstructive pulmonary disease. Table 46 below shows the summary tabulation of the SAEs by SOC in the secondary safety pool.

Table 46: SAEs by SOC in the Secondary Safety Pool

System Organ Class Preferred Term	Plecanatide 3 mg N =1417 n (%) E	Plecanatide 6 mg N = 3072 n (%) E	Placebo N = 1180 n (%) E
Number of patients with SAEs and number of events	24 (1.7) 29	41 (1.3) 51	18 (1.5) 19
Cardiac disorders	2 (0.1) 2	2 (0.1) 4	0
Ear and labyrinth disorders	1 (0.1) 1	0	0
Gastrointestinal disorders	2 (0.1) 2	4 (0.1) 4	0
General disorders and administration site	1 (0.1) 1	2 (0.1) 2	2 (0.2) 2
Hepatobiliary disorders	0	2 (0.1) 2	0
Immune system disorders	0	1 (0.0) 1	0
Infections and infestations	2 (0.1) 2	5 (0.2) 6	5 (0.4) 5
Injury, poisoning and procedural	0	5 (0.2) 6	1 (0.1) 1
Investigations	4 (0.3) 4	5 (0.2) 6	1 (0.1) 1
Musculoskeletal and connective tissue	0	0	1 (0.1) 1
Neoplasms benign, malignant and unspecified	1 (0.1) 1	3 (0.1) 3	0
Nervous system disorders	2 (0.1) 2	3 (0.1) 3	0
Pregnancy and perinatal conditions	4 (0.3) 5	8 (0.3) 9	3 (0.3) 4
Psychiatric disorders	1 (0.1) 1	0	0
Renal and urinary disorders	1 (0.1) 2	2 (0.1) 2	1 (0.1) 1
Reproductive system and breast disorders	0	0	0
Respiratory, thoracic and mediastinal	1 (0.1) 1	2 (0.1) 2	1 (0.1) 1
Vascular disorders	1 (0.1) 1	1 (0.0) 1	3 (0.3) 3

Source: Adapted from Sponsor's Table 5, 120-Day Safety Update Report (May 27, 2016). Post-text Table 14.3.1.3.1.2.1; Includes duplicate patients and those from sites #362 and #402 from study SP304203-03

Reviewer Comment: The overall rates of serious adverse events are low and the proportions were similar across treatment arm. Pregnancy appears to be the most commonly reported "SAE" in the plecanatide treated patients. Of note, in the entire safety data base, there were no reported SAEs of diarrhea, dehydration, or ischemic colitis, with are potential AEs of concern for plecanatide. The proportion of elevated hepatic enzymes events were reported at a higher rate in the plecanatide treatment than placebo group under the Investigations SOC and are discussed further in the review in the Laboratory Finding section. These findings support as favorable risk profile for plecanatide.

SAEs Possibly Related to Study Drug

A total of four patients were considered to have SAEs that were possibly related to the study-drug in the plecanatide development program, secondary safety pools. Two SAEs in the primary pool were considered possibly related to study drug by the sponsor and/or investigator. One of these patients was in the placebo group and reported the CTCAE grade 2 AE of acute diverticulitis of the sigmoid colon (Patient 317-107). The second was a patient in the plecanatide 6 mg group with CTCAE grade 3 AE of liver function test abnormality/ elevated LFTs (Patient 253-210). This case is discussed further in Laboratory Findings, Section 8.4.6.

In the three other studies that comprise the secondary safety pool, there were two SAEs that were considered possibly related to the study drug by the sponsor and/or investigator. In the phase 3, open-label extension study, two SAEs in the 120-day update were reported to be considered related to the study drug. One of these patients, who had elevation of AST levels (Patient 366-216), is discussed in Laboratory Findings, Section 8.4.6. The second case (Patient 481-501) was a patient with ECG changes which were considered to possibly study-drug related and is discussed below.

Reviewer comment: Since Patient 317-107 reported to experience diverticulitis while receiving placebo treatment, this reviewer finds that this event was not caused by the study drug. Please see the comments on the other, aforementioned cases below.

(1) *Patient 481-501: ECG changes*, plecanatide 6mg, SP304203-01

A 49-year-old female, randomized to plecanatide 6mg QD in study SP304203-01 with long-standing history of hypertension, experienced abdominal pain and diarrhea since the start of the study and acute nausea and vomiting on Day 26 and Day 29. The patient had ECG changes on Day 31, which required hospitalization. Concomitant medications included amlodipine 10 mg orally QD and hydrochlorothiazide (HTCZ) 25 mg orally QD. In the hospital, an ECG showed sinus tachycardia, nonspecific ST and T wave abnormality, interpreted by the ECG machine as possible lateral or inferior ischemia. A repeat ECG a few minutes later, showed sinus tachycardia, T-wave abnormality, and possible lateral or inferior ischemia. Physical examination findings were within normal limits with the exception of slight abdominal tenderness. Laboratory results showed multiple abnormalities, including decreased electrolytes and elevated AST (125 IU/L), ALT (82 IU/L), potassium (2.9 mEq/l), and magnesium (1.7 mg/dl) which required supplementation. The patient was ultimately discharged from the hospital in stable condition.

The investigator assessed the event ECG change as moderate in intensity and having a reasonable possibility of a relationship to the study treatment. Consequently, in view of the patient's ECG changes, the investigator elected to terminate her study participation. Multiple attempts to contact the patient after discharge were unsuccessful and final outcome of the event is unknown. The sponsor assessed the event as unexpected and unrelated to study drug. The ECG findings were nonspecific ST-T wave changes in a 49 year-old woman with long-standing hypertension, but no prior heart disease. These were probably related to dehydration and electrolyte abnormalities which followed (a) chronic diuretic use (HCTZ) for hypertension and (b) several days of rapid onset, moderate-to-severe nausea and vomiting after one month of study drug administration that was adequately tolerated.

Reviewer comment: This reviewer agrees with the sponsor that the plecanatide most likely did not cause the potential cardiac ischemia directly and the resultant ECG findings in this case. However, the patient's diarrhea caused by plecanatide, along with the use of a diuretic, may have created her electrolyte imbalance or further worsened such an imbalance. This may have contributed to this patient's symptomatology and EKG changes. In this case, diarrhea could have possibly been considered as an SAE given the patient's outcome.

SAEs Considered Non-Study Drug Related

SAEs of Elevated Hepatic Enzymes

Elevated hepatic enzymes were considered "Medically Important Events" reported as SAEs in cases in which:

1. Aminotransferases (ALT or AST) are > 3 times the upper limit of normal (ULN) with an associated elevation of Total Bilirubin > 2 times ULN without evidence of hemolysis or with alkaline phosphatase (AKP) < 2 times ULN (or not available), or
2. ALT or AST activity that is greater than 5 times the upper limit of normal.

PTs that are possibly related to these events include AEs of elevated hepatic enzymes PTs labeled as abnormal liver function tests and elevated ALT and/ or AST levels.

In the primary pool, there were six SAE cases of elevated hepatic enzymes which met the definition for medically important event (Patients 742-112, 231-212, 415-209, 445-202, 269-203 and 253-210) in patients receiving plecanatide and one in patients receiving placebo (patient 402-228). Patient 269-203 was not originally reported as having SAE of elevated hepatic enzymes at the time of the NDA submission and this was discovered during the review

period. In the additional three studies that comprise the secondary pool, four additional patients were identified in patients receiving plecanatide (Patients 626-106, 408-106, 366-216, and 753-501). Cases of elevated hepatic enzymes are discussed further in Laboratory Findings, Section 8.4.6.

Other SAEs (Gastrointestinal) Cases of Interest

Other gastrointestinal SOC SAEs that are thought to be unrelated to the study-drug are described below:

(1) *Patient 691-102: Acute Pancreatitis*, plecanatide 6mg QD, SP304203-00:
A 39-year-old female was admitted to the hospital with abdominal pain for two days consistent with the clinical diagnosis of acute pancreatitis (Day 48) which completely resolved the next day. The study drug was permanently discontinued on Day 46 due to abdominal pain and the patient was withdrawn from the study on Day 52. The patient's relevant medical history included gallstones and minimal alcohol intake. During the hospitalization, she had documented elevation of lipase to 133 U/L (NR: 22-51 U/L) while amylase levels had not been performed. Her abdominal CT scan and ultrasound was unremarkable. The laboratories at the study visits show an elevation in amylase and lipase then resolution at the last visit (Day 71).

The investigator and sponsor assessed the event as moderate in intensity with no reasonable possibility of relationship to study drug. Per the principal investigator, the reported event was related to the patient's history of gallstones. The sponsor further noted that although acute gallstone pancreatitis could not be conclusively ruled in or ruled out, the clinical presentation, laboratory results, imaging results, and clinical course were not diagnostic of acute pancreatitis.

Reviewer comment: It appears that the episode of possible pancreatitis may be unrelated to treatment drug since the patient had a history of gallstones, which may have caused the patient's symptomatology.

(2*) Patient 141-105: Intestinal Obstruction and Hemorrhagic Ascites*, plecanatide 3mg QD, SP304203-00:
A 69-year-old male developed intestinal obstruction requiring hospitalization and diagnostic laparoscopy which showed adhesions from prior abdominal hernia repair surgeries surgery. The SAE of the intestinal obstruction resolved following laparoscopic adhesiolysis of adhesion from previous. The investigator and sponsor assessed the intestinal obstruction as severe in intensity with no reasonable possibility of relationship to study drug. In the opinion of the

principal investigator, the event of intestinal obstruction was related to adhesions and the hemorrhagic ascites was secondary to the intestinal obstruction surgery.

Reviewer Comment: It appears that the episode of intestinal obstruction is unrelated to treatment drug as the patient had a history of adhesions from prior abdominal surgery.

8.4.3. Dropouts and Discontinuations Due to Adverse Effects

Primary Safety Pool Patient Disposition

A total of 2343 patients (83.9%) in the primary pool completed the study, when including duplicate patients and those from sites #362 and #402 from study SP304203-03. However, 101 patients (3.6%) discontinued study drug because of an AE. Although patient disposition categorizations were similar across treatment groups, a higher percentage of 3mg and 6 mg plecanatide group patients than placebo group patients discontinued due to because of AEs (4.2%, 4.4% and 2.2%, respectively). Inversely, a higher percentage of placebo patients than plecanatide patients discontinued because of insufficient therapeutic effect (2.4% versus 0.6%). Please see Table 47 for details of patient disposition in the primary safety pool.

Table 47: Patient Disposition in the Primary Safety Pool

Patient Disposition	Placebo (N = 924) n, %	Plecanatide	
		3 mg (N = 941) n, %	6 mg (N = 926) n, %
ITT-S Population, n (%)	924 (100.0)	941 (100.0)	926 (100.0)
Completion Status, n (%)			
Completed the study	786 (85.1)	777 (82.6)	780 (84.2)
Discontinued from the study	138 (14.9)	164 (17.4)	146 (15.8)
Reason for Discontinuation, n (%)			
Adverse event	20 (2.2)	38 (4.0)	41 (4.4)
Death	0	0	0
Insufficient therapeutic effect	22 (2.4)	7 (0.7)	4 (0.4)
Lost to follow-up	17 (1.8)	23 (2.4)	17 (1.8)
Noncompliance with study drug	2 (0.2)	1 (0.1)	1 (0.1)
Physician decision	2 (0.2)	1 (0.1)	0
Protocol violation	19 (2.1)	25 (2.7)	24 (2.6)
Patient withdrawal of consent	27 (2.9)	45 (4.8)	36 (3.9)
Other	29 (3.1)	24 (2.6)	23 (2.5)

Source: Adapted from Sponsor's Table 12, ISS. Post-text Table 14.1.1.1, Including duplicate patients and those from sites #362 and #402 from study SP304203-03.

Reviewer comment: This reviewer finds that the slightly higher discontinuation rate in the plecanatide treatment group versus the placebo group for the AEs for adverse events appears reasonable and expected. Accordingly, the discontinuations due to lack of treatment effect is higher in the placebo than the plecanatide groups, which makes sense and is reassuring in regards to the perception of the efficacy of plecanatide in the treatment of CIC.

Types of AEs Leading to Discontinuation

The following excludes duplicate patients and those from sites #362 and #402 from study SP304203-03:

Eleven (non-pregnancy) SAEs in the primary safety pool resulted in discontinuation of study drug. Four events were reported in the 3 mg plecanatide group (intestinal obstruction, cerebral infarction, renal cancer, and vertigo positional); three events were reported in the 6 mg plecanatide group (staphylococcal infection, chronic obstructive pulmonary disease, liver function test abnormal); and four of these were reported in the

placebo group (femoral neck fracture, intervertebral disc protrusion, arterial occlusive disease, and nephrolithiasis.

The most frequently reported SOC of all AEs leading to discontinuation in the 3mg and 6mg plecanatide groups versus the placebo group was gastrointestinal disorders (3.1% and 3.5%, vs. 0.7% respectively). As expected, in the primary safety pool, the 3 mg and 6 mg plecanatide groups had a greater frequency of gastrointestinal events leading to discontinuation than the placebo group (2.9% and 3.2%, respectively, versus 0.6%).

The most frequently reported preferred terms of AEs leading to discontinuation in the combined plecanatide groups versus the placebo group were diarrhea (35 patients 2%) and abdominal pain (7 patients, 0.4%). All other preferred terms were reported by 3 or fewer plecanatide patients. While the incidences of diarrhea and abdominal pain leading to discontinuation were low, they were higher in the combined plecanatide group than in the placebo group (1.9% versus 0.4% for diarrhea; 0.4% versus 0.1% for abdominal pain). See Table 48 for the common AEs leading to treatment discontinuation in the primary safety pool.

Table 48: Common AEs Leading to Treatment Discontinuation in the Primary Safety Pool

Adverse Events (AEs) n, %	Plecanatide 3 mg (N = 863) n (%)	Plecanatide 6 mg (N = 868) n (%)	Placebo (N = 870) n (%)
Number of patients with any AE leading to discontinuation	38 (4%)	42 (5%)	20 (2%)
Diarrhea	18 (2%)	17 (2%)	4 (0.5%)
Abdominal pain	3 (0.3%)	4 (0.5%)	1 (0.1%)
Vomiting	2 (0.2%)	0	0
Abdominal distension	2 (0.2%)	1 (0.1%)	0

Source: Reviewer's Table, derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2; Excluding duplicate patients and those from sites #362 and #402 from study SP304203-03.

Secondary Safety Pool Patient Discontinuation

A total of 263 patients (4.7%) in the secondary pool discontinued study drug because of an AE. The percentage of patients with these events in the combined plecanatide group was higher than in the placebo group (5.3% versus 2.5%). The most frequently reported SOC mirrored those of the primary pooled safety analysis. Although the incidences of

the most frequently reported events were low, the plecanatide treatment group had a higher incidence than the placebo group of diarrhea (2.7% versus 0.4%), abdominal distension (0.2% versus 0.1%), fecal incontinence (0.1% versus 0), and flatulence (0.1% versus 0%).

From the 120-day update study data, at the completion of the open-label, extension study SP304203-01, the sponsor reported a total of 125 patients (5.3%) experienced AEs that led to discontinuation of study drug, with the incidence being similar between the 3 mg and 6 mg plecanatide groups (6.3% and 5.2%, respectively).

Reviewer comment: This reviewer finds that the higher rate of diarrhea-related AEs leading to discontinuation in the plecanatide groups versus. the placebo group is expected and is appropriate to place in the label. In addition, although the numbers are small, the plecanatide group had more discontinuations due to abdominal pain related AEs. These abdominal pain related AEs include, in part, the AEs of abdominal distension and abdominal pain, which would be expected to occur with plecanatide treatment given the known mechanism of action of the drug and the reasonable adverse reactions to the drug. The incidences of discontinuations were similar in the secondary pooled patients as they were in the primary pool patients. This lends to the generalizability of the data to the CIC population from the primary safety pool.

8.4.4. Significant Adverse Events

Primary Safety Pool

The maximum severity of an AE was categorized as mild, moderate, or severe based on the investigator's grading of the event. Excluding duplicate patients and those from sites #362 and #402 from study SP304203-03, of the 811 patients reporting AEs in the primary safety pool, a total of 56 patients experienced at least one severe AE. The incidence of severe AEs was slightly higher in the 3mg and 6mg plecanatide group than in the placebo group (2.3%, 2.6% versus 1.4%).

The most frequently reported severe AEs in the combined plecanatide group were diarrhea (16 patients, 1%) and abdominal pain (6 patients, 0.3%). All other severe AEs occurred in 2 or fewer patients. The incidence of severe diarrhea was higher in the combined plecanatide group than in the placebo group (1% versus 0.3%), and was also higher in the 6 mg plecanatide dose group than in the 3 mg plecanatide dose group (1.3% versus 0.6%). The incidence of severe abdominal pain was similar across treatment arms.

Table 49 provides an overview of severe AEs by treatment arm in the primary safety pool.

Table 49: Severe Adverse Events Occurring in ≥ 2 Patients in the Primary Safety Pool

Severe Adverse Events N=2601 n (%)	Plecanatide		Placebo (N = 870)
	3 mg QD (N = 863)	6 mg QD (N = 868)	
Total Number patients with Severe AEs	20 (2.3%)	23 (2.6%)	13 (1.5%)
Diarrhea	5 (0.6%)	11 (1.3%)	3 (0.3%)
Abdominal distension	2 (0.2%)	0	1 (0.1%)
Abdominal pain	3 (0.3%)	3 (0.3%)	2 (0.2%)
Abdominal pain upper	0	1 (0.1%)	1 (0.1%)

Source: Reviewer's Table, derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2, Excluding duplicate patients and those from sites #362 and #402 from study SP304203-03.

Diarrhea: To determine if there was an imbalance in significant diarrhea associated with plecanatide treatment, and due to the increased rate of discontinuation of AE for diarrhea in the plecanatide treatment arms versus placebo, Table 50 below summarizes the AE of diarrhea from the primary safety pool by severity, categorization as serious, and whether they lead to discontinuation.

Table 50: Overall Adverse Events Analysis of Diarrhea in the Primary Safety Pool

AEs of Diarrhea N=2601	Plecanatide 3 mg QD (N=863) (n, %)	Plecanatide 6 mg QD (N=868) (n, %)	Placebo QD (N=870) (n, %)
Overall AEs of Diarrhea	43 (5.0%)	47 (5.4%)	11 (1.3%)
Leading to Discontinuation	2.1%	2.0%	0.5%
Categorized as Serious			
yes	0	0	0
no	43	47	11
Categorized as Severe			
yes	5 (0.6%)	11 (1.3%)	3 (0.3%)
no	38	36	8

Source: Reviewer's Table; derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2, Excluding duplicate patients and those from sites #362 and #402 from study SP304203-03.

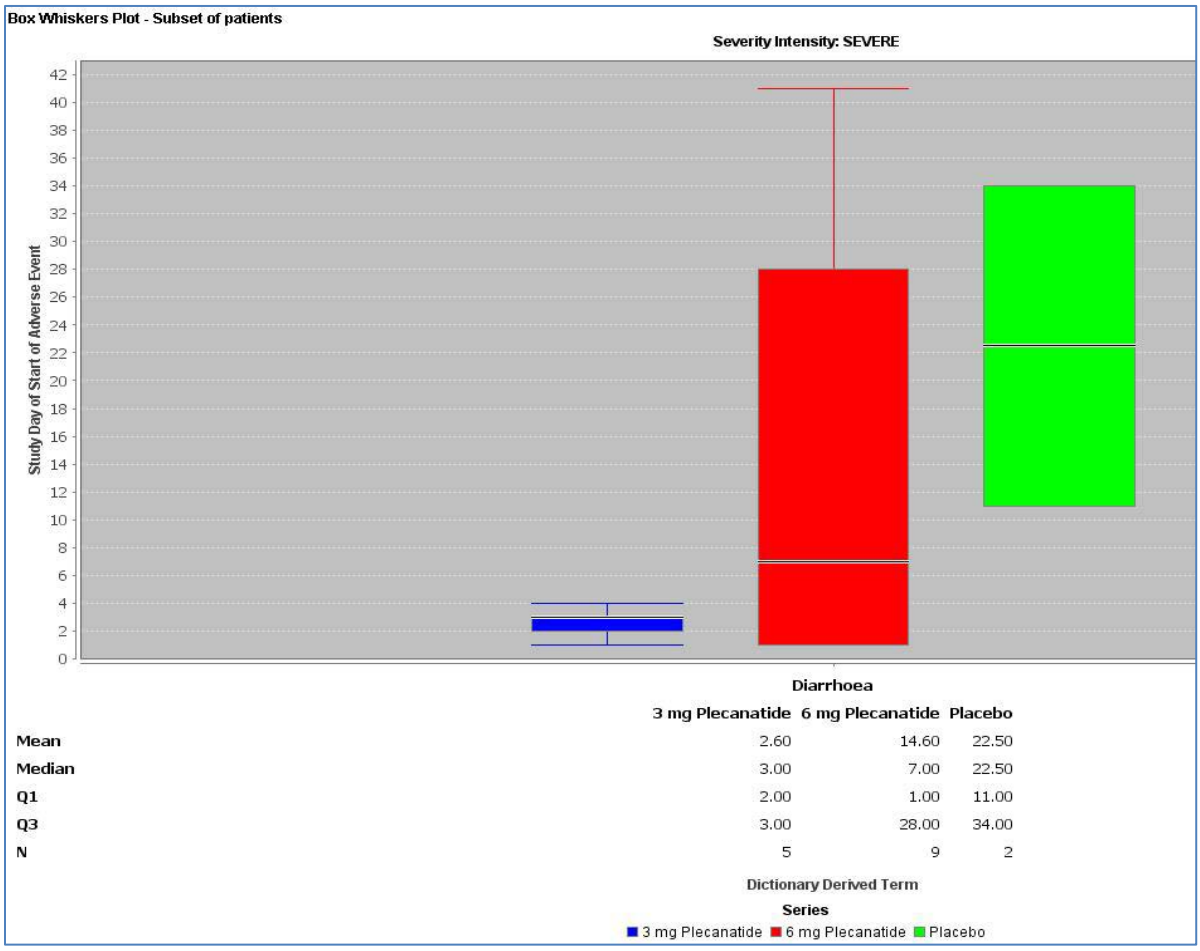
Reviewer comment: This reviewer believes that the higher rate of severe diarrhea in the plecanatide treatment arms in comparison to the placebo arm is not unexpected and is likely related to the mechanism of action of the drug. Of note, although the numbers were small and the percentage of severe adverse events appears equal between the plecanatide groups, the adverse event of severe diarrhea was reported twice as much in the plecanatide 6mg group versus the plecanatide 3mg group. In addition, this reviewer believes the patient who suffered from an SAE of ECG changes possibly should have been considered to have a severe AE and an SAE of diarrhea.

In the secondary safety pool, the incidences of severe AEs were similar between the placebo and combined plecanatide groups (2.3% and 2.9%, respectively) and between the 3 mg and 6 mg plecanatide dose groups (2.8% and 2.7%, respectively). However, the incidences of severe diarrhea was higher in the combined plecanatide group than in the placebo group. Between the two plecanatide treatment groups, the 6 mg plecanatide group had a higher incidence of severe diarrhea in comparison to the 3 mg plecanatide dose group (1.0% versus 0.3%). This finding may indicate that the higher dose of plecanatide less tolerable than the lower dose of the drug. Of note, there were no severe AEs of dehydration or orthostatic hypotension, as seen with linaclotide, as the same class of medication.

Severe Diarrhea Timing

For patients who received plecanatide 3mg in the primary safety pool and experienced severe diarrhea, this adverse event occurred within the first three days of the study treatment. As an AE of interest, the timing of severe diarrhea occurrence was examined in Figure 10.

Figure 10: Timing of Severe Diarrhea in Primary Safety Pool



Source: Reviewer's Graph, derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2
Excluding duplicate patients and those from sites #362 and #402 from study SP304203-03.

<u>Reviewer comment:</u> Based on the data presented in the table above, the reported occurrence of AEs decrease over time. Notably, the AE of diarrhea was reported early (<4 weeks) in the course of treatment in the plecanatide groups and all cases of severe AEs of diarrhea were reported in the first few days of plecanatide treatment. It is interesting the severe diarrhea as reported to occur earlier in time in the plecanatide 3mg versus 6mg group overall, although the numbers of patients who presented with severe diarrhea were low and the data may be skewed and this observation may be simply by chance occurrence.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

There were fairly equal proportions of patients with any AE and serious AEs in plecanatide treatment arms versus the placebo arm. No deaths occurred in any arm in these phase 3 studies. There was a higher proportion of AEs attributed to the study drug in the treatment arms versus the placebo arm, and more severe adverse events in the plecanatide groups. Likewise, there were more discontinuations due to adverse events in the treatment arms vs. the placebo arm, which were mostly due to diarrhea.

Table 51: Overview of Adverse Events Analysis in the Primary Safety Pool

Adverse Events (AEs) n, (%)	Treatment Weeks 1-12					
	Plecanatide 3mg (N=941)		Plecanatide 6 mg (N=926)		Placebo (N=924)	
Patients with any AE	288	(30.6%)	288	(31.1%)	265	(28.7%)
Possible Attribution to the Study Drug/ Placebo	66	(7.0%)	73	(7.9%)	36	(3.9%)
Patients with Severe AEs	21	(2.2%)	23	(2.5%)	13	(1.4%)
Patients with any Serious AEs (SAEs)	14	(1.5%)	9	(1.0%)	12	(1.3%)
Patients with any AEs Leading to Death	0	(0)	0	(0)	0	(0)
Patients with any AEs Leading to Permanent Treatment Discontinuation	39	(4.1%)	42	(4.5%)	20	(2.2%)

Source: Reviewer's Table, derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2; Including duplicate patients and those from sites #362 and #402 from study SP304203-03.

Reviewer comment: The proportion of patients who reported any AEs were fairly equal across the treatment groups. However, approximately two times more AEs in the plecanatide group were attributed to the study drug than the placebo group. This indicates that more non-specific AEs may have affected patients in the placebo group and more plecanatide-specific, GI-related AEs, due to the drug's mode of action, affected those in the plecanatide group. Accordingly, twice as many AEs in general led to treatment discontinuation in the plecanatide treatment arm versus the placebo arm. Although the discontinuation rate was low, this finding suggests that patients who took plecanatide found it more difficult to tolerate due to drug- related AEs than those in the placebo group.

Table 52: Common AEs (>1% of Patients) in Primary Safety

Adverse Event (PT) N=2601	Plecanatide 3 mg N=863 n (%)	Plecanatide 6 mg N=868 n (%)	Placebo N= 870 n (%)
Diarrhea	43 (5.0%)	47 (5.4%)	11 (1.3%)
Headache	16 (1.9%)	16 (1.8%)	18 (2.1%)
Urinary tract infection	14 (1.6%)	13 (1.5%)	16 (1.8%)
Sinusitis	12 (1.4%)	6 (0.7%)	3 (0.3%)
Upper respiratory tract infection	12 (1.4%)	5 (0.6%)	10 (1.1%)
Abdominal distension	10 (1.2%)	8 (0.9%)	3 (0.3%)
Flatulence	9 (1.0%)	8 (0.9%)	5 (0.6%)
Nasopharyngitis	9 (1.0%)	20 (2.3%)	14 (1.6%)

Source: Reviewer's Table, derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2, Excluding duplicate patients and those from sites #362 and #402 from study SP304203-03

Reviewer comment: In the primary safety pool, there are more AEs of diarrhea seen in the plecanatide treatment group than in the placebo group. Additionally, the AEs of sinusitis, upper respiratory tract infection, abdominal distention and flatulence occur more often in the plecanatide treatment group than the placebo arms.

Timing of Diarrhea AE Occurrence

Table 53: Time Period of AEs in the Primary Safety Pool

Time to Onset Preferred Term	Placebo (N = 924) n (%)	Plecanatide			Overall (N = 2791) n (%)
		3 mg (N = 941) n (%)	6 mg (N = 926) n (%)	Combined (N = 1867) n (%)	
≤4 weeks					
Number of patients with AEs	113 (12.2%)	147 (15.6%)	142 (15.3%)	289 (15.5%)	402 (14.4%)
Diarrhea	1 (0.1%)	34 (3.6%)	36 (3.9%)	70 (3.7%)	71 (2.5%)
>4 weeks to ≤8 weeks					
Number of patients with AEs	91 (9.8%)	79 (8.4%)	102 (11.0%)	181 (9.7%)	272 (9.7%)
Diarrhea	5 (0.5%)	7 (0.7%)	8 (0.9%)	15 (0.8%)	20 (0.7%)

Source: Reviewer Table, Adapted from Sponsor's ISS Table 28, Including duplicate patients and those from sites #362 and #402 from study SP304203-03

Reviewer comment: *Based on the data presented in the table above, the reported occurrence of AEs decrease over time. Notably, the AE of diarrhea was reported early (< 4weeks) in the course of treatment in the plecanatide groups and all cases of severe AEs of diarrhea were reported in the first few days of plecanatide treatment. As discussed earlier, it is interesting that severe diarrhea was reported earlier during treatment in the plecanatide 3mg vs. 6mg group overall, although the numbers of patients who presented with severe diarrhea were low and the data may be skewed.*

Overview of AEs in the Secondary Safety Pool

The safety results of the secondary safety pool were consistent with those seen in the primary safety pool. Of note, due mainly to diarrhea-related adverse events, there were more discontinuations and patients with severe AEs in the plecanatide 6 mg group than the 3mg group.

8.4.6. Laboratory Findings

Clinical laboratory test results were analyzed for only the primary pool because laboratory assessments in the secondary pool studies differed with respect to timing and/or types of assessments.

Chemistry

Mean and median values and changes from baseline for each chemistry analyte were similar in the 3 mg plecanatide, 6 mg plecanatide, and placebo groups. Laboratory grade levels were classified by the National Cancer Institute-Common Terminology Criteria for Adverse events (CTCAE). At various time points, a greater number of patients in the 3 mg and 6 mg plecanatide groups had at least a 1-grade increase in CTCAE level for neutrophil count, amylase, and urate in comparison to those in placebo group. Table 54 summarizes the proportion of patients in the primary pool with clinical laboratory abnormalities that resulted in at least a 1-grade increase in CTCAE severity from baseline.

Table 54: Clinical Laboratory Abnormalities, Least a 1-Grade CTCAE Increase

	Placebo (N = 924)	Plecanatide			Overall (N = 2791)
		3 mg (N = 941)	6 mg (N = 926)	Combined (N = 1867)	
Number (%) of patients with at least 1 laboratory abnormality with a ≥1-grade shift from baseline [1]	696 (75.3)	701 (74.5)	698 (75.4)	1399 (74.9)	2095 (75.1)
Number (%) of patients with at least 1 laboratory abnormality with a 1-, 2-, 3-, or 4-grade shift from baseline [1]					
1-grade shift	680 (73.6)	686 (72.9)	685 (74.0)	1371 (73.4)	2051 (73.5)
2-grade shift	117 (12.7)	141 (15.0)	131 (14.1)	272 (14.6)	389 (13.9)
3-grade shift	34 (3.7)	25 (2.7)	38 (4.1)	63 (3.4)	97 (3.5)
4-grade shift	6 (0.6)	2 (0.2)	8 (0.9)	10 (0.5)	16 (0.6)
Number (%) of patients with at least 1 missing to any grade shift	3 (0.3)	1 (0.1)	0	1 (0.1)	4 (0.1)

Source: Sponsor's ISS Table 40; [1] baseline value was defined as the last non-missing value collected prior to first dose of study drug. Source: Post-text Table 14.3.7; CTCAE: the National Cancer Institute-Common Terminology Criteria for Adverse events

Reviewer comment: *This reviewer finds that the shifts in the grades of laboratory abnormalities are proportional among all treatment arms. Overall, low percentages of patients had chemistry level elevations and there were inconsistency of findings across time points. Given the low systemic bioavailability of plecanatide, these findings suggest that the chemistry shifts may not be related to the study drug and supports the safety of plecanatide.*

Elevated Hepatic Enzymes: Potential Hy's Law Cases

The following tables below show the shift from baseline values of the hepatic enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and alkaline phosphatase (ALP), respectively, in the primary safety pool. Of potential concern, two patients (Patient 231-212 and 269-203) had elevated hepatic test results that potentially met Hy's law criteria for hepatotoxicity. The cases are described in this section.

Table 55: Alanine Aminotransferase (ALT) Shifts from Baseline in the Primary Safety Pool

Highest Post-Randomization Value	Number (%) of Patient		
	Plecanatide 3mg N=832	Plecanatide 6mg N=841	Placebo N=841
Normal ALT at Baseline			
ALT > 2xULN <=3xULN	4 (0.5%)	9 (1.1%)	2 (0.2%)
ALT > 3xULN <=5xULN	4 (0.5%)	2 (0.2%)	2 (0.2%)
ALT > 5xULN <=10xULN	1 (0.1%)	1 (0.1%)	0
ALT > 10xULN <=15xULN	1 (0.1%)	0	0
Abnormal ALT at Baseline			
ALT > 2xULN <=3xULN	7 (0.8%)	6 (0.07%)	9 (1.1%)
ALT > 3xULN <=5xULN	2 (0.2%)	1 (0.1%)	2 (0.2%)
Total ALT Elevations	18 (2.2%)	19 (2.3%)	15 (1.8%)

Source: Adapted from Sponsor's table 14.3.3.2.1 from IR response 9/16/16;
Only subjects with both a baseline and post-baseline ALT results are included in the table.

Table 56: Aspartate Aminotransferase (AST) Shifts from Baseline in the Primary Safety Pool

Highest Post-Randomization Value	Number (%) of Patient		
	Plecanatide 3mg N=841	Plecanatide 6mg N=832	Placebo N=901
Normal AST at Baseline			
AST > 2xULN <=3xULN	2 (0.2%)	1 (0.1%)	2 (0.2%)
AST > 3xULN <=5xULN	1 (0.1%)	3 (0.3%)	3 (0.3%)
AST > 5xULN <=10xULN	3 (0.3%)	0	0
Abnormal AST at Baseline			
AST > 2xULN <=3xULN	1 (0.1%)	2 (0.2%)	1 (0.1%)
AST > 3xULN <=5xULN	1 (0.1%)	0	0
Total AST Elevations	8 (1.0%)	6 (0.7%)	6 (0.7%)

Source: Adapted from Sponsor's table 14.3.3.2.2 from IR response 9/16/16;
Only subjects with both a baseline and post-baseline AST results are included in the table.

Table 57: Bilirubin Shifts from Baseline in the Primary Safety Pool

Highest Post-Randomization Value	Number (%) of Patient		
	Plecanatide 3mg N=832	Plecanatide 6mg N=841	Placebo N=841
Normal Bilirubin at Baseline			
BILI > 2xULN <=3xULN	0	0	0
BILI > 3xULN <=5xULN	2 (0.2%)	0	0
Abnormal Bilirubin at Baseline			
BILI > 2xULN <=3xULN	0	0	1 (0.1%)
Total Bilirubin Elevations	2 (0.2%)	0	1 (0.1%)

Source: Adapted from Sponsor's table 14.3.3.2.4 from IR response 9/16/16;
Only subjects with both a baseline and post-baseline Bilirubin results are included in the table.

Table 58: Alkaline Phosphatase (ALP) Shifts from Baseline in the Primary Safety Pool

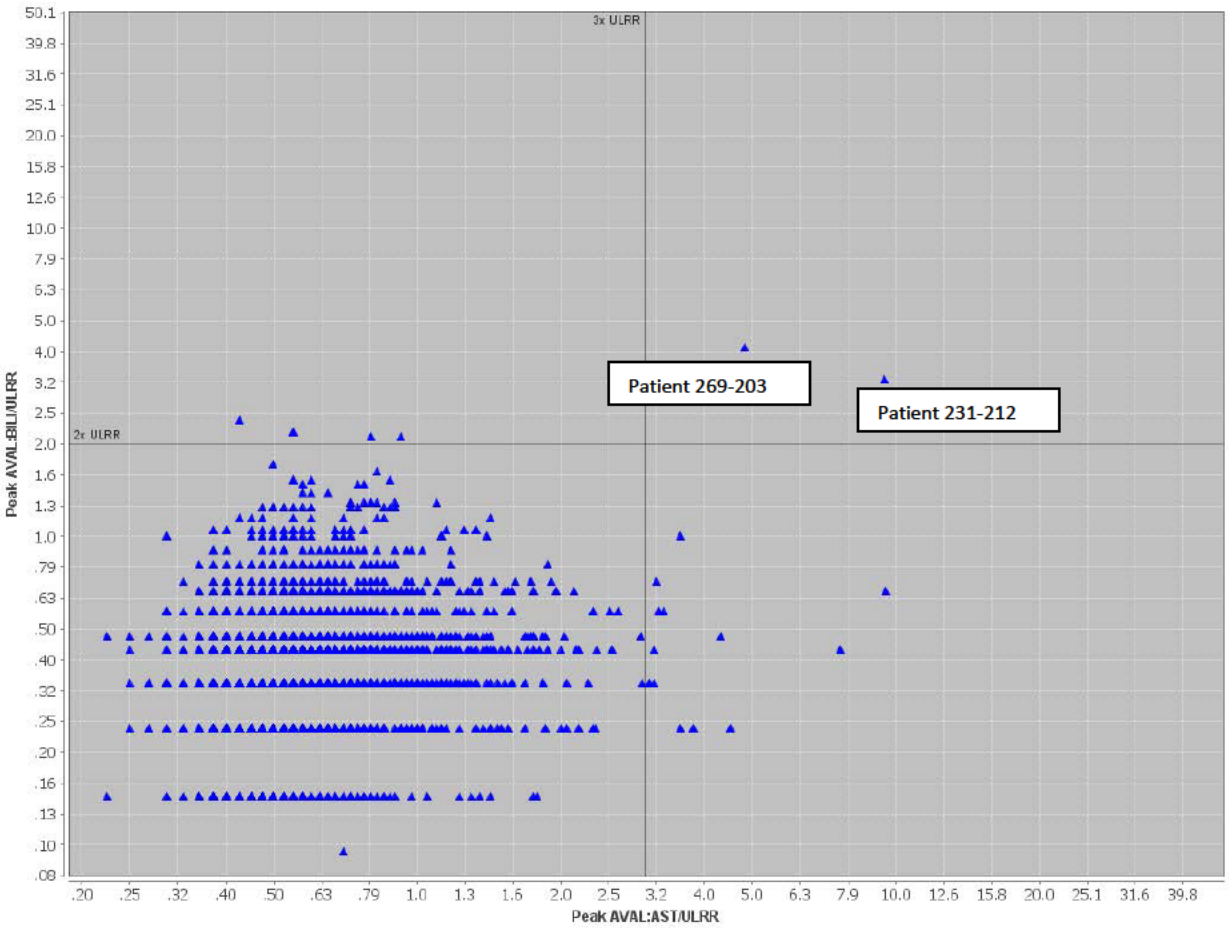
Highest Post-Randomization Value	Number (%) of Patient		
	Placebo N=841	Plecanatide 3mg N=832	Plecanatide 6mg N=841
Normal ALP at Baseline			
ALP > 2xULN <=3xULN	0	1 (0.1%)	0
ALP > 3xULN <=5xULN	0	1 (0.1%)	0
Abnormal ALP at Baseline			
ALP > 2xULN <=3xULN	2 (0.2%)	0	2 (0.2%)
ALP > 3xULN <=5xULN	1 (0.1%)	0	0
Total ALP Elevations	3 (0.3%)	2 (0.2%)	2 (0.2%)

Source: Adapted from Sponsor's table 14.3.3.2.2 from IR response 9/16/16;
Only subjects with both a baseline and post-baseline ALP results are included in the table.

Reviewer comment: Overall, the incidence of patients with post-randomization hepatic enzyme level elevations was small and similar between the plecanatide treatment groups and placebo. This was also the case with the AST and ALP levels as well. In patients who had baseline elevated levels of ALT, AST, Bilirubin and ALP, a small, yet similar, increase in these hepatic enzymes occurred in patients at similar frequencies. This may indicate that patients who have baseline hepatic disease or injury are not adversely affected by plecanatide treatment.

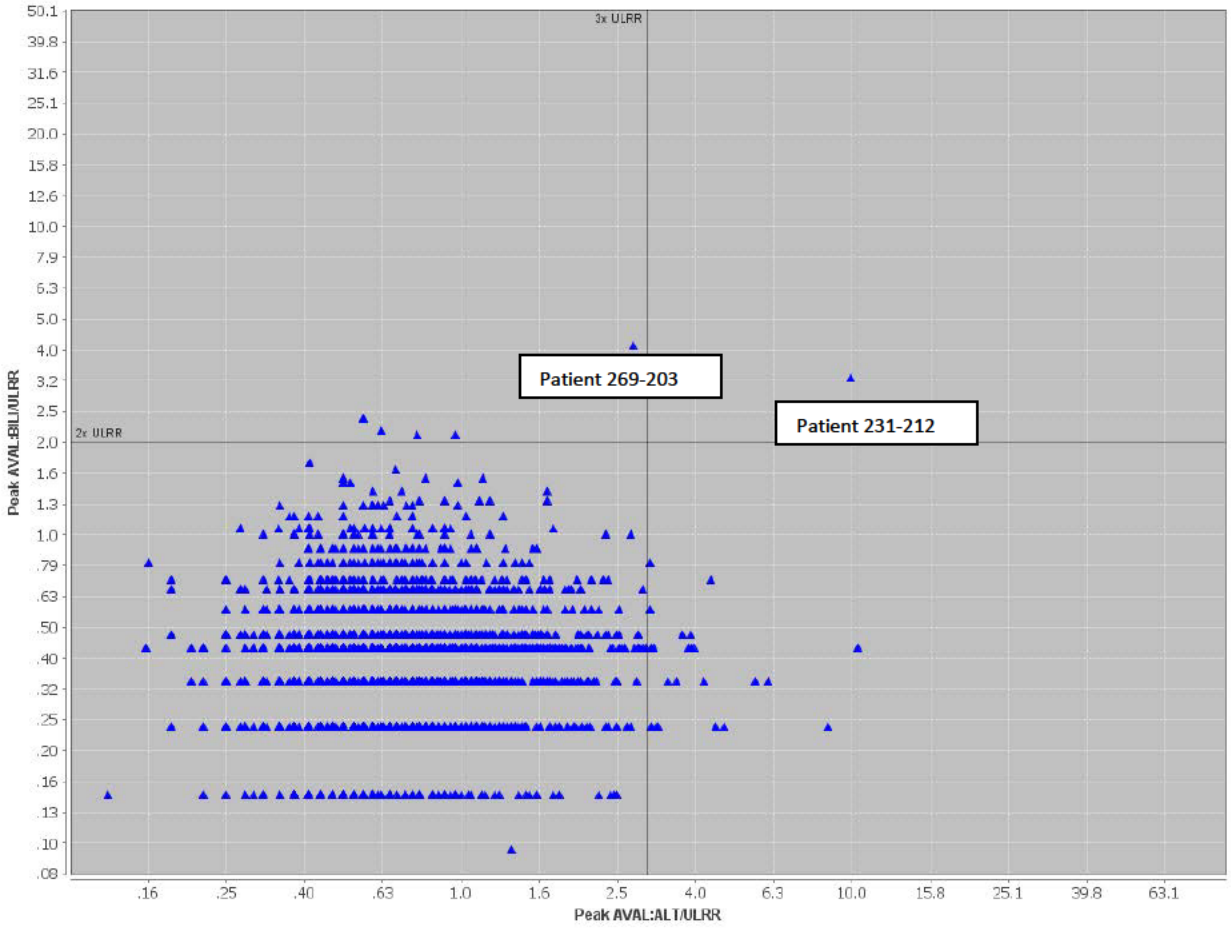
Although the sponsor submitted that there were no cases of Hy's law in the plecanatide clinical development program, this reviewer identified two potential cases. These two patients were in the plecanatide 3mg group and had elevated bilirubin levels >2x ULN in association with elevated ALT and AST > 3x ULN. See Figure 11 and Figure 12 below for the potential Hy's law cases laboratory graphs.

Figure 11: Potential Hy's Law Cases - AST vs. Bilirubin in Primary Safety Pool



Source: Reviewer's Figure, derived from Study -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2

Figure 12: Potential Hy's Law Cases - ALT vs. Bilirubin in Primary Safety Pool



Source: Reviewer's Figure, derived from Study -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2

Narratives of Potential Hy's Law Cases

(1) *Patient 231-212*: Elevated hepatic enzymes, Plecanatide 3mg group, study SP304203-03

A 35-year-old male, with no relevant medical history, experienced an asymptomatic elevation of the hepatic enzymes results at the Week 12 (Day 85) visit, at which time the plecanatide treatment was stopped. The patient reported taking one dose of acetaminophen 1600 of mg for low back pain the day before his visit (day 84). On the day 85, his physical examination was normal and no alcohol consumption, drug use, or smoking was reported. An acetaminophen level was not performed on Day 85 although additional laboratory tests were performed on Day 90. During a right upper quadrant abdominal ultrasound on Day 91, the patient was noted to have cholelithiasis and increased echogenicity of the hepatic parenchyma

consistent with fatty infiltration of the liver. Subsequently, the elevated hepatic enzymes were noted to have returned to normal levels 14 days later at the end of the study (Day 98).
The investigator and sponsor assessed the event of elevated hepatic enzymes as being mild in intensity and showing no possibility of relatedness to study treatment. Per the investigator, acetaminophen use was reported as an alternative cause of the event. See Table 59 and Table 60 for this patient's laboratory details and Figure 13 for his graphical profile below.

Table 59: *Patient 231-212:* Laboratory Results of Elevated Hepatic Enzymes

Visit (Normal Value)	ALT (0 – 44 IU/L)	AST (0 – 40 IU/L)	ALP (42 -107 U/L)	Total Bilirubin (0.1 – 1.2 mg/dL)	Direct Bilirubin (0.0 – 0.4 mg/dL)
Screening	36	27	98	0.9	0.2
Week 1	25	17	87	0.8	0.2
Week 4	136	35	131	0.4	<0.2
Week 8	28	17	106	1	0.2
Week 12, EOT Day 85	436	378	160	4	1.9
Unscheduled	298	53	159	0.9	0.3
EOS	41	20	111	1	0.2

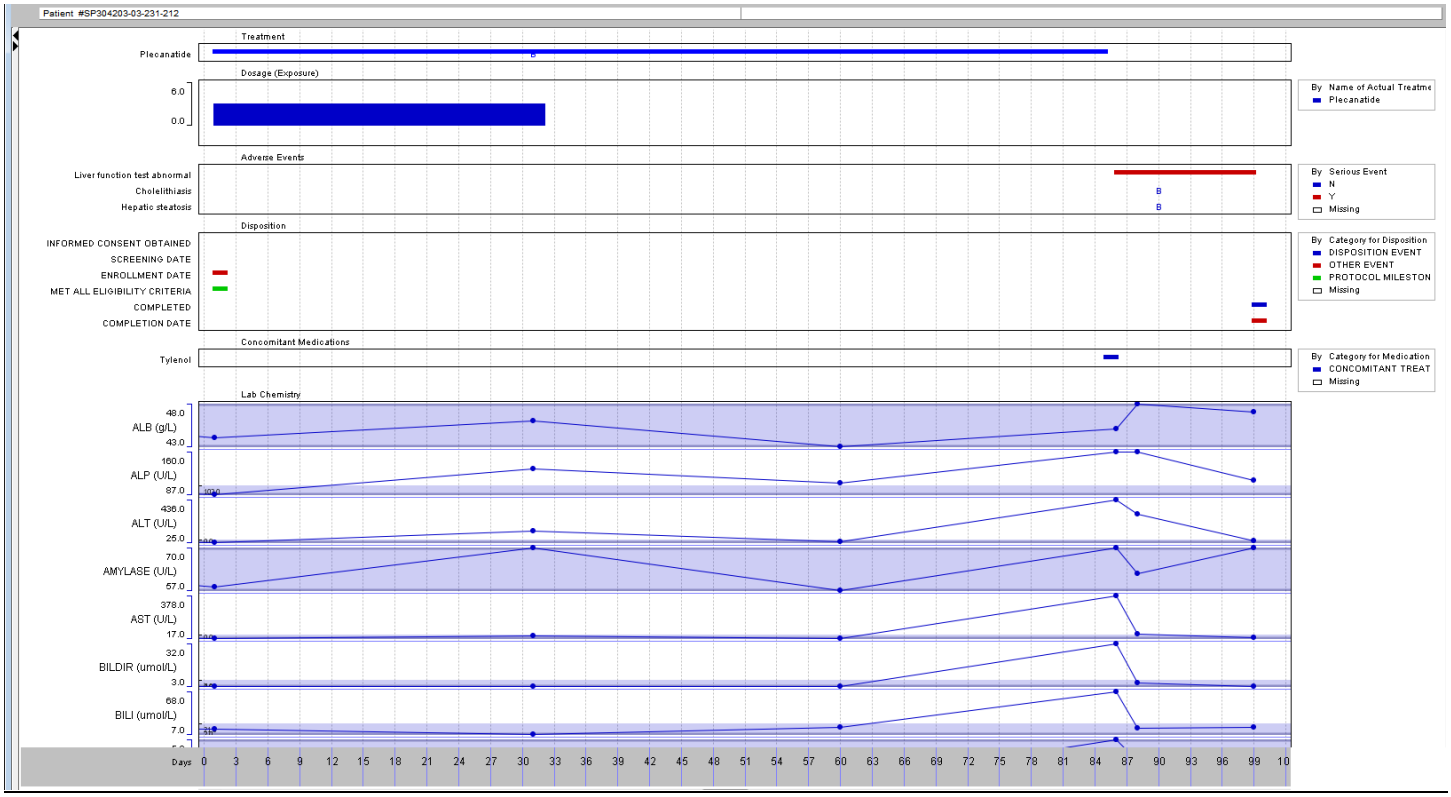
Source: Adapted from Sponsors ISS Narratives, pg. 66/67; ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP= Alkaline phosphatase, EOS = end of study, EOT = end of treatment

Table 60: *Patient 231-212:* Additional Laboratory Results, Day 90

Laboratory Test	Results	Reference Range
GGTP	446 IU/L	7 – 64 IU/L
PT/INR	9.9 sec	9.3 – 11.4 sec
INR	0.95	0.0 – 2.0
PTT	26.8 sec	26 – 40 sec
Hepatitis C	Negative	
Hepatitis A and B	Not measureable due to hemolyzed sample	

Source: Adapted from Sponsors ISS Narratives, GGTP = gamma-glutamyl transferase,
INR = international normalized ratio, PT =prothrombin time, PTT = partial thromboplastin time.

Figure 13: *Patient 231-212:* Patient Profile, Plecanatide 3 mg, SP304203-03



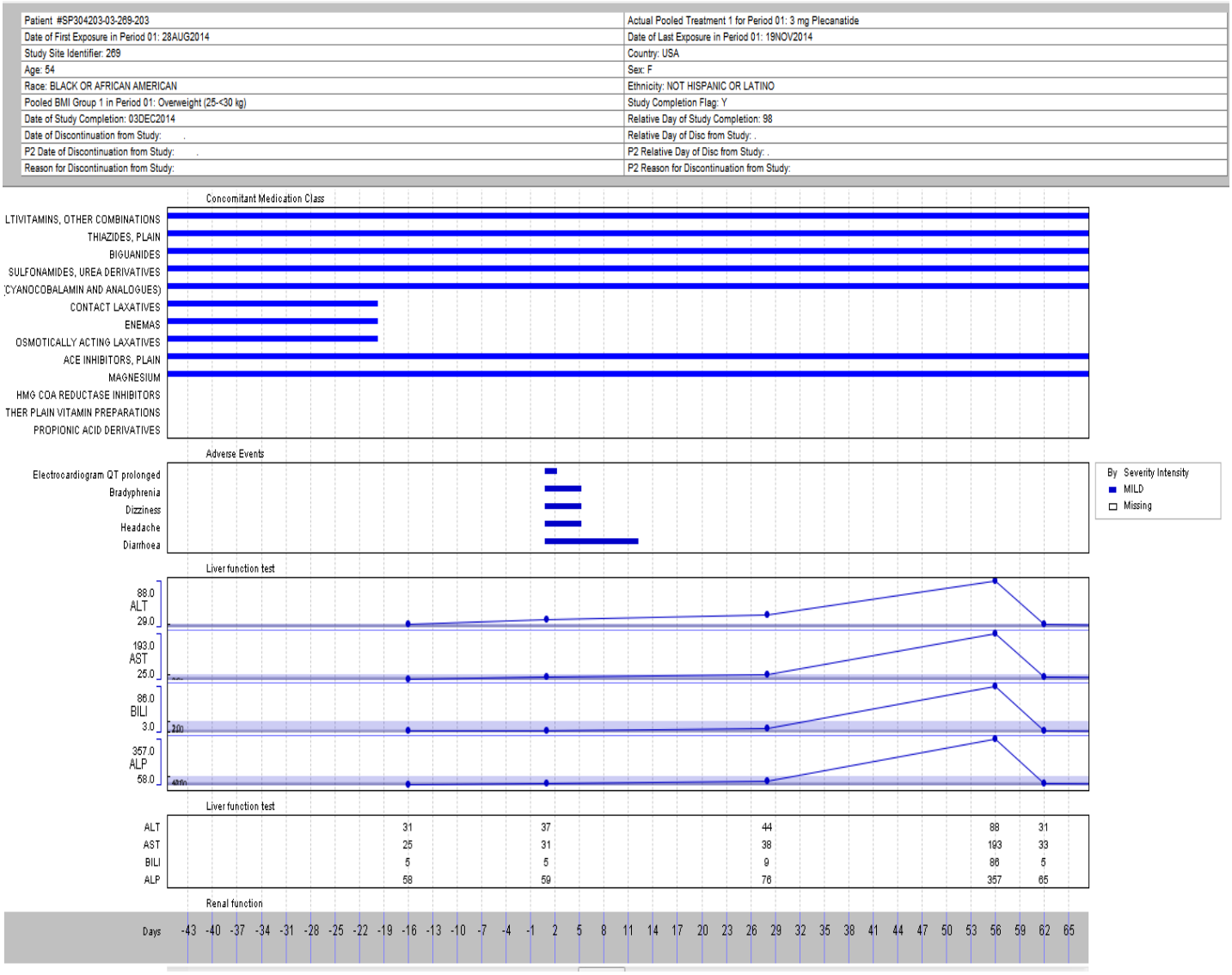
Source: Reviewer's Figure, derived from Study -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2

<u>Reviewer comment:</u> This reviewer agrees plecanatide probably did not caused the increase in the liver enzymes of ALT and AST > 3 x ULN and Bilirubin > 2 times ULN. Although this case is concerning for the potential of meeting Hy's Law, this patient reported taking a supra-therapeutic dose of acetaminophen the day prior to the scheduled Week 12 laboratory tests, As a concomitant medication and particularly at a high dose, acetaminophen is known to cause liver injury. The patient also had elevated GGT and ALP which indicates that the patient also suffered from cholestatic liver disease, possibly in relationship to cholelithiasis, fatty liver disease, or another disease process, given the patient's finding on ultrasound.

(2) *Patient 269-203*: Plecanatide 3mg group, SP304203-03

A 54-year-old female, with medical history significant for type 2 diabetes mellitus and dyslipidemia and associated medical therapy, experienced an asymptomatic elevation of the hepatic enzymes results at the Week 8 visit. The laboratory abnormalities had returned to normal 6 days later and the patient continued the study drug without interruption for a total of 12 weeks. See Figure 14 and for the patient graphical profile below.

Figure 14: *Patient 269-203:* Patient Profile, Plecanatide 3mg group, SP304203-03



Source: Reviewer's figure, derived from Study -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2

Table 61: *Patient 269-203:* Elevated Hepatic Enzymes

Laboratory Tests		
Test/ Normal Range (NR)	**Date – Visit**	**Result**
ALT NR: 0 – 32 U/L	11 Aug 2014 –Screening	31
	28 Aug 2014 – Week 1 (Day 1)	37
	24 Sep 2014 – Week 4	44
	22 Oct 2014 – Week 8	88
	28 Oct 2014 – Unscheduled Visit 50.3	31
	19 Nov 2014 – Week 12 (EOT)	29
	03 Dec 2014 – Week12 (EOS)	30
AST NR: 0 – 40 U/L	11 Aug 2014 –Screening	25
	28 Aug 2014 – Week 1 (Day 1)	31
	24 Sep 2014 – Week 4	38
	22 Oct 2014 – Week 8	193
	28 Oct 2014 – Unscheduled Visit 50.3	33
	19 Nov 2014 – Week 12 (EOT)	26
	03 Dec 2014 – Week12 (EOS)	28
ALK NR: 42 – 107 U/L	11 Aug 2014 –Screening	58
	28 Aug 2014 – Week 1 (Day 1)	59
	24 Sep 2014 – Week 4	76
	22 Oct 2014 – Week 8	357
	28 Oct 2014 – Unscheduled Visit 50.3	65
	19 Nov 2014 – Week 12 (EOT)	58
	03 Dec 2014 – Week12 (EOS)	61
Total Bilirubin NR: 2 – 21 umol/L	11 Aug 2014 –Screening	5
	28 Aug 2014 – Week 1 (Day 1)	5
	24 Sep 2014 – Week 4	9
	22 Oct 2014 – Week 8	86
	28 Oct 2014 – Unscheduled Visit 50.3	5
	19 Nov 2014 – Week 12 (EOT)	3
	03 Dec 2014 – Week12 (EOS)	5
Direct bilirubin NR: 0 – 7 umol/L	11 Aug 2014 –Screening	<3
	28 Aug 2014 – Week 1 (Day 1)	<3
	24 Sep 2014 – Week 4	<3
	22 Oct 2014 – Week 8	<3
	28 Oct 2014 – Unscheduled Visit 50.3	<3
	19 Nov 2014 – Week 12 (EOT)	<3
	03 Dec 2014 – Week12 (EOS)	<3

ALK = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate aminotransferase, EOS = end of study,

Source: Sponsor's IR August 24, 2016

Reviewer comment: Based on this reviewer's safety analysis of the data, information about this patient was requested in an IR from the sponsor since this patient was not originally reported as an SAE. The sponsor admits that this patient should have been reported by the investigator as an SAE and this information should have been reported at the time of NDA submission. Upon review of this patient's details, this reviewer believes that this patient does not meet Hy's law due to the concomitant elevation of alkaline phosphatase values. In

addition, the patient remained on therapy without interruption and the elevated hepatic enzyme levels returned to baseline values. This suggesting the one time elevated hepatic enzyme values are most likely spurious and are due to laboratory error. The patient remained asymptomatic and was able to complete the study.

Other Hepatic Enzyme Elevation Cases

Of note, there were no SAEs of increased hepatic enzymes in studies SP304201-09 or SP30420210. Table 62 provides a summary of elevated hepatic enzyme SAEs in the secondary safety pool from studies SP304203-00, SP304203-03, and SP304203-01.

Table 62: Summary of Elevated Hepatic Enzyme SAEs

Study	Treatment Group	Patient Case	Preferred Terms Provided	Severity Grade CTCAE (per SAE)	Potential Hy's Law Case	Related/ unrelated per Sponsor	Plausible Cause	Action Taken with Study Drug
SP304203-00								
	Plecanatide 3mg QD	742-112	Elevated AST And ALT	3	No	No	Unclear, also had hematuria and proteinuria, see narrative	None
	Plecanatide 3mg QD	149-132	Increased ALT and AST (at baseline)	none	No	No, not reported as an SAE	At baseline	Stopped
SP304203-03								
	Placebo QD	402-228	ALT increase	1	No	No	Unclear, asymptomatic early withdrawal due to non-compliance	None
	Plecanatide 3mg QD	232-212	Elevated AST ALT total Bilirubin, ALP)	1	Yes	No	Concomitant supra-therapeutic of Tylenol dose	None, occurred at end of treatment. Normalized by EOS visit
	Plecanatide 3mg QD	415-209	Elevated AST and ALT	2	No	No	Unknown cause, resolution of elevation 13 days later, no discontinuation of medications	None

	Plecanatide 3mg QD	445-202	Elevated ALT/ Cholecystitis	2/ 2	No	No	Gallbladder disease	None
	Plecanatide 3mg QD	269-203	Liver Function Test Abnormal (Elevated AST, ALT, total Bilirubin, ALP)	None	Yes	No Not reported as an SAE,	Concomitant simvastatin, HCTZ, Lisinopril, glimepiride, metformin, and ibuprofen prn, possible acute ETOH abuse or gallstone passing per sponsor	None, patient remained on therapy, LFTs normalized (likely lab error)
	Plecanatide 6mg QD	253-210	Elevated LFTs	3	No	Reasonable possibility of a relationship – per investigator/ Unrelated per Sponsor	Concomitant Indomethacin and OCPs	Stopped
SP304203-00/ SP304203-01								
	Plecanatide 6mg QD	626-106	ALT and AST increased	None	No	Reasonable possibility of a relationship not reported as an SAE	Elevated levels at end of -00 study and then again in -01 study	Stopped
SP304203-03/ SP304203-01								
	Plecanatide 6mg QD	408-106	Elevated ALT/ Elevated AST	3/ 3	No	No	History of alcohol abuse, using alcohol in study, Concomitant Simvastatin	Stopped
	Plecanatide 6mg QD	366-216	Abnormal AST/ ALT and ALP	3	No	Reasonable possibility of a relationship per investigator/ Unrelated per Sponsor	Concomitant Losartan, took 5 more pills than instructed, elevated at EOT (week 12) of -03 study and then elevated at early termination (day 51 of study -01), resolved 5 days after drug stopped	Stopped
SP304203-01 (no previous study)								
	Plecanatide 6mg QD	753-501	ALT Increased/ AST and ALP	1	No	No	Baseline elevations at screening, Concomitant	None

							gabapentin chronically	

Source: Reviewer's Table, based on Sponsor's IR responses and narratives from studies SP304203-00, -03, and -01

Study Drug Related SAEs with Elevated Hepatic Enzymes in the Primary Safety Pool

Per a study investigator, there was one study-drug related case in the primary safety pool:

(1) *Patient 253-210*: Plecanatide 3mg, SP304203-03

A 45-year-old female had asymptomatic elevated hepatic enzyme results that met criteria for an SAE on Day 56. Elevations occurred on Day 56 of treatment and plecanatide was discontinued on Day 59. Subsequent lab assessment on Day 59 showed continued elevations, however, an unscheduled assessment 93 days later showed normalization of the labs. No relevant medical history for the SAE was reported. Concomitant medications included three months of indomethacin 25 mg PO BID for a groin injury and birth control pills as a hormone replacement. Relevant laboratory values are presented in the Table 63 below.

Table 63: *Patient 253-210:* Laboratory Results of Elevated Hepatic Enzymes

		Test Results				
		ALT (IU/L)	AST (IU/L)	Alk Phos (U/L	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)
Date	Visit	NR: 0 – 32	NR: 0 – 40	NR: 432-107	NR: 0.1 – 1.2	NR: 0.0 – 0.4
9/26/2014	Screening	9	12	74	0.3	< 0.2
10/14/2014	Baseline	8	13	69	0.2	< 0.2
11/18/2014	Week 4	97	42	55	0.2	< 0.2
12/9/2014	Week 8 (local lab)	193	83	57	0.2	< 0.2
	Week 8 (central lab)	278	151	Not Done	Not Done	N/A
12/22/2014	Early Withdrawal	317	188	57	0.3	< 0.2
1/14/2015	Unscheduled	13	16	69	0.1	< 0.2

ALT = alanine aminotransferase, AST = aspartate aminotransferase, N/A = not applicable, NR = normal range.
Note: No laboratory results were reported at the PCP Follow-up Visit on 12 Jan 2015.
Source: Adapted from Sponsor's CSR 14.3.3. Narratives

The investigator assessed the event elevated LFTs as severe in intensity and having a reasonable possibility of relatedness to study drug. However, the sponsor disagreed with the investigator's assessment. The sponsor's rationale was that the chronic usage of indomethacin served as another potential cause for the elevated LFTs and the elevated

LFTs did not resolve upon discontinuation of study drug at the early withdrawal visit. This SAE was initially reported to the regulatory authorities based on the more conservative investigator's assessment of causality but the final causality assessment reflected the sponsor's determination.

Reviewer comment: *This reviewer agrees with the sponsor's stated rationale regarding cases of elevated hepatic enzymes.*

Primary Safety Pool SAEs of Elevated Hepatic Enzymes Non-Related to Study Drug

There were additional five (5) patients who were reported to have abnormal hepatic enzyme levels, which resolved and were not considered to be related to the study drug. Four of these cases involved patients in the plecanatide 3mg group (one of which occurred during screening) and one in the placebo group. Brief presentations of three narratives of the patients who received plecanatide treatment group are discussed below:

(1) *Patient 742-112*: Elevated AST, plecanatide 3mg QD, study SP304203-00

A 20 year old male experienced an asymptomatic elevation of the AST level which met SAE criteria. The lab abnormality was resolved 12 days later. Concomitant medications included olanzapine and levomilnacipran. Prior to the SAE of increased AST, the patient had experienced transient elevated ALT. The event was assessed as mild in intensity and having no reasonable possible relationship to study drug. Thirty days after the last dose of study drug, laboratory tests were performed and showed that the patient's AST level was 381 IU/L, which was over five times above the upper limit of normal and resolved a few days later. At this time, a physical examination was performed and was reported as normal. During the time of the SAE, the patient also experienced blood and protein in the urine. The blood in urine was assessed as moderate and the proteinuria was assessed as mild in intensity. The investigator and sponsor assessed the SAE as severe in intensity and having no reasonable possibility of relationship to study drug. Per the principal investigator, the alternate cause for the event was unknown. See Table 64 below for patient's laboratory results.

Table 64: *Patient 742-112*: Elevated AST

Date	Test	Results	Normal Range
14 Mar 2015	ALT	89 IU/L	0 – 44 IU/L
	AST	381 IU/L	0 – 40 IU/L
	ALP	64 IU/L	44 – 102 IU/L
	Total bilirubin	0.8 mg/dL	0.0 – 0.4 mg/dL
	Bilirubin conjugated	0.2 mg/dL	0.1 – 1.2 mg/dL
25 Mar 2015	ALT	63 IU/L	0 – 44 IU/L
	AST	31 IU/L	0 – 40 IU/L
	ALP	59 IU/L	44 – 102 IU/L
	Total bilirubin	0.2 mg/dL	0.0 – 0.4 mg/dL
	Bilirubin conjugated	< 0.2 mg/dL	0.1 – 1.2 mg/dL
24 Apr 2015	ALT	20 IU/L	0 – 44 IU/L
	AST	13 IU/L	0 – 40 IU/L
	ALP	64 IU/L	44 – 102 IU/L
	Total bilirubin	1.0 mg/dL	0.0 – 0.4 mg/dL
	Bilirubin conjugated	0.3 mg/dL	0.1 – 1.2 mg/dL

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase.

Source: Adapted from Sponsor's CSR 14.3.3 Narratives, pg. 12/106

(2) *Patient 415-209*: Elevated AST, plecanatide 3mg QD, study SP304203-03

A 43 year old male experienced an asymptomatic elevation of the AST level of 306 IU/L at the End of Treatment (EOT) Visit, Day 86, that met criteria for an SAE. The patient's medical and surgical history included hyperlipidemia and no concomitant medications were reported. The patient's AST levels were reportedly within normal limits previously and when repeated 2 weeks later at the End of Study Visit. The event elevated AST was reported as resolved 13 days later on Day 98. The investigator and sponsor assessed the increased AST as moderate in intensity and having no reasonable possibility of relatedness to study treatment.

(3) *Patient 445-202*: Cholecystitis and Elevated ALT, Plecanatide 3mg QD, study SP304203-03

A 41-year-old female experienced two SAEs including cholecystitis and increased ALT. The patient's medical and surgical history included gastric bypass surgery and no concomitant medications were reported. First AE: On Day 43, the patient underwent a laparoscopic cholecystectomy with laparoscopic lysis of adhesions. The patient was discharged home in stable condition. All liver function tests were normal during her hospitalization. Following symptomatic treatment and laparoscopic cholecystectomy, the patient improved and the cholecystitis resolved on Day 43. The investigator and sponsor assessed the event as moderate in intensity and having no reasonable possibility of

relatedness to study treatment. Second SAE: On Day 55, at Visit 3, an asymptomatic elevation of the ALT (5x ULN) was found that met criteria for an SAE. The study drug was permanently discontinued on Day 69. No symptoms or additional medications were reported at this time. The patient was temporarily lost to follow-up, but resolved on Day 312 when the patient returned for an unscheduled visit and the ALT was determined to be within the normal range. The investigator and sponsor assessed the event as moderate in intensity and having no reasonable possibility of relatedness to study treatment. During the investigation of cholecystitis, it was discovered that the patient had previously undergone gastric bypass surgery and on Day 69, the principal investigator elected to early terminate the patient because of this protocol violation. See Table 65 below for the patient's laboratories.

Table 65: *Patient 445-202*: Cholecystitis and Elevated ALT, Plecanatide 3mg QD

Test Date	Visit	Test	Result	Normal Range
28 Aug 2014	Visit 3/Week 1	ALT	23 IU/L	0 – 32 IU/L
		AST	23 IU/L	0 – 40 IU/L
		AP	43 IU/L	42 – 107 IU/L
22 Oct 2014	Visit 5/Week 8	ALT	240 IU/L	0 – 32 IU/L
		AST	41 IU/L	0 – 40 IU/L
		AP	193 IU/L	42 – 107 IU/L
05 Nov 2014	Early Termination	ALT	330 IU/L	0 – 32 IU/L
		AST	75 IU/L	0 – 40 IU/L
		AP	239 IU/L	42 – 107 IU/L
06 Jul 2015	Unscheduled	ALT	41 IU/L	Within Normal Range

ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase.
Source: Adapted from Sponsor's CSR 14.3.3 Narratives

Review's comment: Upon the evaluation of these patient narratives, this reviewer finds that it was appropriate to believe that the majority of SAEs that were deemed by the sponsor as not related to the study drug are, indeed, most likely not related. Given the low number, the type of SAEs, and the fact that patients recovered from the SAEs in the plecanatide treatment group were reassuring.

Overall, elevated liver enzymes tests, including elevated AST and ALT was the most commonly reported SAE in plecanatide treated patients, occurring 6 times in the 3mg plecanatide vs. once in the 6mg plecanatide and placebo group in the primary safety pool. Although this reviewer believes that it is difficult to draw any specific conclusions at this time, this reviewer does believe that the inclusion of elevated hepatic enzymes into the labeling are warranted and routine postmarketing monitoring is appropriate.

120-Safety Update SAEs: Elevated Hepatic Enzymes

There were three cases of elevated liver enzymes in patients of the plecanatide 6mg group that were reported as SAEs during the treatment phase of the study SP304203-01. See Table 62 for descriptions of the cases. Two of these patients experienced elevate hepatic enzyme levels at the end of their initial 12 week study in SP304203 -03, had normalization of the enzymes, and then a repeat increase in the levels during treatment in the long-term SP304203-01 study. There is a potential concern in these cases that these liver enzyme elevations were caused by concomitant medications, which also may effect hepatic enzyme levels , respectively. Fortunately, in these cases and in other patient in the safety update, elevations of hepatic enzymes did not meet the definitions for Hy's Law.

Hematology

The number of patients with shifts in hematology labs was similar across treatment groups. The overall low number of patients with these shifts and the lack of this finding at other time points suggest that factors other than study drug may have contributed to the treatment group differences.

8.4.7. Vital Signs

Vital signs were analyzed for only the primary safety pool since these assessments differed across studies in the secondary pool with respect to timing. The placebo, 3 mg plecanatide, and 6 mg plecanatide groups showed comparable results for each vital sign measurement and the changes from baseline at each study visit. No concerning trends were observed over time.

Reviewer comment: This reviewer believes that there is no evidence of clinically meaningful changes in vital signs in patients who were treated with plecanatide.

8.4.8. Electrocardiograms (ECGs)

ECG results were analyzed for only the primary pool because these assessments differed across studies in the secondary pool with respect to timing. Patients were evaluated for shifts in ECG assessments in heart rate, PR, QRS, QT, QTcB, and QTcF intervals from normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS) at baseline to normal, abnormal (NCS), or abnormal (CS) at Day 1 post-treatment, week 12 (EOT), and week 14 (EOS) or Early Withdrawal (EW).

Electrocardiogram results were categorized as whether or not clinically significant (per the

sponsor) findings were present. No patient had clinically significant ECG findings at baseline. On Day 1, four patients in the placebo group and one in the 3 mg plecanatide group, had shifts to clinically significant ECG findings. At Week 14, seven patients in the placebo group, six patients in the 3 mg plecanatide group, and one patient in the 6 mg plecanatide group had shifts to clinically significant ECG findings. In those who received plecanatide, these changes included the occurrence of one of more of the following in each patient: transient T-wave abnormalities (n=2), ST-segment elevation (n=2), QTc prolongation per ECG machine (n=1), premature ventricular contractions (n=2), accelerated junctional rhythm (n=1), sinus bradycardia (n=2) that were not associated with chest pain, subsequent myocardial infarction or other sequelae. One patient experienced ECG changes that were attributed to plecanatide, as discussed in The SAE section 8.4.2 above.

8.4.9. QT Interval

Because plasma concentrations of plecanatide and its major metabolite SP-338 are negligible or not detectable following administration of clinically relevant oral doses, the Agency agreed to a waiver of Thorough QT (TQT) evaluation.

8.4.10. Immunogenicity

Blood samples for anti-plecanatide antibody testing were collected from all patients in the phase 3 CIC clinical development program. The sampling times were Week 0 (prior to study drug exposure), Week 4, Week 12 (Study SP304203-01 only), Week 14 (Studies SP304203-00 and SP304203-03), Week 28 (Study SP304203-01 only), Week 52 (Study SP304203-01 only), and Week 72 (Study SP304203-01 only). The screening assay for anti-plecanatide antibodies has been validated, however the sponsor stated that testing of these samples was delayed, awaiting correction of instrumentation issues. Immunogenicity testing of plasma samples from the phase 3 clinical studies is ongoing at the time of this review. Potential adverse reactions associated with immunogenicity include hypersensitivity reactions and reactions associated with the theoretical uroguanylin depletion (UDP) syndrome caused by cross reactions of possible anti-plecanatide antibodies with endogenous guanylin peptides. These are discussed further in Section 8.5.3 below.

<u>Reviewer comment:</u> In regards to immunogenicity, although plecanatide is a minimally absorbed small peptide product, it has attributes that make it potentially immunogenic. Ideally, adequate assays to adequately assess the rate of anti-plecanatide antibody formation would have been developed and validated for use during the plecanatide development program. Linaclotide (another GC-C agonist with similar structure) is currently developing and validating such assays . A PMR will likely need to be incorporated to address any insufficiencies at the time of approval, per the Division of OBP. See the reviews by Clinical

Pharmacologist Dr. Dilara Jappar and OBP reviewer Dr. Haoheng Yan for the review of the immunogenicity.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Diarrhea and Drug Class Related AEs

Please refer to Section 8.4.4 above, under Significant Adverse Events for further details on diarrhea specific AEs.

Reviewer comment: ***Diarrhea*** *is discussed previously in Section 8.4.4*

8.5.2. CIC Treatment Class Concerns

Reviewer comment: Ischemic colitis was identified as a potential risk with other CIC treatments and was assessed during this clinical review. There were no reports of ischemic colitis during plecanatide clinical development. However, there were a few cases of AEs that could be associated with ischemic colitis that were reported in fairly equal frequency among treatment groups. These AEs include anal hemorrhage, fecal discoloration, rectal hemorrhage or hematochezia, and collectively, two patients in the 3mg group, seven patients in the 6mg group, and six in the placebo group reported these AEs in the secondary safety pool. An occurrence of ileus was reported in one placebo group patient and intestinal obstruction occurred in one plecanatide treated patient as discussed above.

The frequency of gastroenteritis was similar among all groups. There was one confirmed case of Clostridium difficile colitis in the 6mg plecanatide group. Of the secondary safety pool, anemia was reported in 4 cases in the 3mg and placebo group and in 12 cases of the 6mg group. There were two cases of mild hemoglobin/ hematocrit decreased in the 6mg group. However, it is unlikely that ischemic colitis occurred in patients treated with plecanatide since the proportion of patients with these ischemic colitis-related AE are fairly similar among the groups. The following AEs were not seen in the analysis of the results of 5 studies of secondary safety pool: melena, occult blood positive, rectal hemorrhage. Overall, this reviewer identified no signal for ischemic colitis in the plecanatide clinical development program. Additionally, there were no reported incidences of SAEs of diarrhea, dehydration, nor fecal incontinence, which is supportive for the plecanatide risk profile.

8.5.2 Abdominal Pain-Related AEs

In this review analysis, this reviewer has combining PTs that are related to abdominal pain in order to determine the collective incidence of abdominal pain-related adverse events. These PT terms include the following: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal distention, and abdominal tenderness. See Table 66 below for the rates in the primary safety pool, excluding duplicate patients and sites #362 and 402.

Table 66: Primary Safety Pool: Abdominal Pain-Related Symptoms

Patients with Abdominal Pain Related AEs			
Gastrointestinal AEs	**Plecanatide 3mg (N=863)**	**Plecanatide 6mg (N=868)**	**Placebo (N=870)**
Abdominal discomfort	2 (0.2%)	2 (0.2%)	1 (0.1%)
Abdominal distension	10 (1.2%)	8 (0.9%)	3 (0.3%)
Abdominal pain	6 (0.7%)	11 (1.3%)	8 (0.9%)
Abdominal pain lower	1 (0.1%)	1 (0.1%)	2 (0.2%)
Abdominal pain upper	5 (0.6%)	3 (0.3%)	4 (0.5%)
Abdominal tenderness	3 (0.3%)	4 (0.5%)	0 (0%)
Total patients per Treatment	27 (3.1%)	29 (3.3%)	18 (2.1%)

Source: Reviewer's Table, derived from Study -00 and -03 Analysis Adam datasets: ADAE and ADSL; JReview 9.2,
Excludes duplicate patients and sites #362 and #402

Reviewer comment: Abdominal pain-related events occur in more than 2% of the patients in the plecanatide treatment group. The frequency of this combined term should be considered for inclusion in the label. When the AE of Abdominal distension is removed, the abdominal pain-related AEs are n=17(2.0%) of patients in the plecanatide 3mg group and n=15 (1.7%) of patients in the placebo group.

8.5.3 Immunogenicity and Uroguanylin Peptide Depletion Syndrome

As previously stated, plecanatide has the potential to be immunogenic and assays are under development to determine the levels of anti-drug antibodies (ADAs) in patients receiving plecanatide. A single SAE of drug hypersensitivity reaction was recorded in a patient (063-506 of study SP304203-01) in the plecanatide 6mg group who took penicillin for a tooth infection and had a subsequent allergic reaction. There were no hypersensitivity reactions per the sponsor that were found to be related to the study drug. As previously stated, plecanatide may also have the potential to lead to immune reactions since it shares structural homology with endogenous uroguanylin.

Theoretically, the development of ADAs may develop and have the potential to cross-react with endogenous guanylin peptides leading to uroguanylin peptide depletion (UPD) syndrome.

A similar concern was identified during the review of Linzess (linaclotide) under NDA 202811. Per the Division Director review by Dr. Griebel, dated August 29, 2012, the reviewers from Division of Therapeutic Proteins/Office of Biotechnology Products (DTP/OBP) were consulted regarding the need for further immunogenicity evaluation of Linzess. The OBP reviewers noted that although Linzess is a small peptide, it has multiple attributes that make it potentially immunogenic, including its 3 disulfide bonds, which render a more rigid tertiary structure than is typical for a 14 amino acid peptide. The ideal T cell epitopes for activation via HLA class 2 pathways are 12-18 amino acids in length, and for the HLA class 1 pathway the epitopes are at least 9 amino acids in length. Therefore, Linzess contains an appropriate number of amino acids to serve as a T cell epitope for either pathway. Due to the structural homology of endogenous guanylin peptide family members, the OBP reviewer said the greatest risk, in terms of safety, if anti-Linzess antibodies were to develop, would be cross reaction with endogenous peptides that could lead to deficiency syndromes. For this reason, it was recommended that the applicant should develop assays for IgM, IgA, and IgG anti-drug antibodies, and that patient samples should be tested for evidence of these antibodies.

Symptoms associated with UPD syndrome include symptoms of fluid overload that include hypertension, hypernatremia, weight gain and edema. Pancreatitis and pancreatic enzyme deficiency are also potential symptoms that may be associated with UPD syndrome. There was only one case of pancreatitis reported in the primary safety pool. A similar concern was raised with linaclotide during clinical development and is currently being assessed as a postmarketing requirement.

Table 67 shows a tabulation of potential UPD syndrome AEs, including data from the 120-day safety update, in the secondary safety pool.

Table 67: Uroguanylin Peptide Depletion (UPD) Syndrome Potential AE, Secondary Safety Pool

Body System/ Organ Class	Preferred Term	Placebo N=1180 n (%)	Plecanatide 3 mg N=1417 n (%)	Plecanatide 6 mg N=3072 n (%)
Cardiac/ Respiratory	CHF	0	1 (0.1%)	1 (<0.1%)
	Dyspnea	1 (0.1%)	0	4 (0.2%)
	Dyspnea exertional	0	0	2 (0.1%)
	Pulmonary Congestion	1 (0.1%)	1 (0.1%)	1 (<0.1%)
General disorders	Edema	0	1 (0.1%)	0
	Peripheral Edema	5 (0.4%)	9 (0.6%)	10 (0.4%)
Investigations	Weight increased	2 (0.2%)	3 (0.3%)	5 (0.2%)
	Blood pressure increased	0	1 (0.1%)	0
Vascular Disorders	Hypertension	12 (1.0%)	10 (0.7%)	14 (0.5%)
Metabolism and nutrition	Fluid retention	0	0	1 (<0.1%)
	Hypernatremia	0	0	1 (<0.1%)
Musculoskeletal	Joint effusion	0	0	2 (0.1%)
	Joint swelling	0	1 (0.1%)	3 (0.1%)
Renal and Urinary	Renal Failure acute	0	0	2 (0.1%)

Source: Review's Table, derived from Updated ISS Analysis Adam datasets: ADAE and ADSL; JReview using the 120 day updated dataset

Reviewer comment: *This reviewer believes that there are no clear signals or obvious differences in the frequency of the potential UPD syndrome adverse events between the plecanatide treatment and the placebo group. Language regarding UPD syndrome is not warranted for labeling at this time. The development of validated anti-plecanatide antibody assays and assessment of the development of ADA responses will be required in the post-marketing setting.*

Potential Weight Gain

Sudden weight gain has also been identified as a potential AE associated with UPD syndrome. The tables below contain information on the weight gain of patients in both the primary and secondary safety pools. Weight increases appear to be proportional across treatment groups. There does not

appear to be a signal for weight increase seen in the plecanatide treatment program.

Table 68: Weight Changes from Baseline in the Primary Safety Pool

Maximum Percent Weight change from Baseline	Placebo N= 924 n (%)	Plecanatide 3 mg N=941 n (%)	Plecanatide 6 mg N=926 n (%)
≤ 5 % weight gain	531 (57.5%)	550 (58.5%)	525 (56.7%)
> 5 – 10 % weight gain	43 (4.7%)	46 (4.9%)	38 (4.1%)
>10 % weight gain	11 (1.2%)	9 (1.0%)	12 (1.3%)

Source: Review's Table, derived from updated Analysis Adam datasets: ADVS WT weight datasets and ADSL; JReview 9.2; Includes sites #362 and #402

Table 69: Weight Changes from Baseline in Secondary Safety Pool

Maximum Percent Weight change from Baseline	Placebo N= 1180 n (%)	Plecanatide 3 mg N=1355 n (%)	Plecanatide 6 mg N=2118 n (%)
≤ 5 % weight gain	532 (45.1%)	553 (40.8%)	901 (42.5%)
> 5 – 10 % weight gain	42 (3.6%)	47 (3.5%)	73 (3.5%)
>10 % weight gain	11 (1.0%)	9 (0.7%)	21 (1.0%)

Source: Review's Table, , derived from updated, Analysis Adam datasets: ADVS WT weight datasets and ADSL , JReview 9.2

Reviewer comment: There are no obvious differences in the percentage of potential UPD syndrome AEs, including weight gain, seen in the plecanatide groups vs. the placebo group. In addition, narratives of these patients were requested and reviewed. Although no safety signals were identified that are consistent with adverse events from uroguanylin peptide depletion, the consideration of post-marketing surveillance for these signals may be warranted.

8.6. Safety Analyses by Demographic Subgroups

Gender

Similar to the primary safety pool analysis, the majority of the patients (81.7% overall) in the secondary safety pool were female. In the secondary safety pool. the combined plecanatide group's incidence of AEs was 28.0% in males and 35.7% in females, and the distribution was generally similar in the placebo group (22.3% males; 32.9% females). Male and female patients in the combined plecanatide group showed generally similar incidences of AEs considered related to study

drug (7.0% males; 10.1% females), AEs leading to discontinuation (4.0% males; 5.6% females), and severe AEs (1.9% males; 3.1% females). Excluding events of pregnancy, the incidence of SAEs was higher in male plecanatide patients than in female plecanatide patients (1.8% versus 0.9%), whereas this difference was not observed in placebo patients (0.9% males; 1.6% females).

The most frequently reported (incidence ≥1.0%) AE preferred terms in female vs. male patients who received plecanatide were diarrhea (6.9% vs. 4.3%), urinary tract infection (2.6% vs. 0.3%), headache (2.3% vs. 1.1%), abdominal pain (1.9% vs. 0.6%), nausea (1.9% vs. 1.8%), upper respiratory tract infection (1.8%), nasopharyngitis (1.6%), abdominal distension (1.6 vs. 0.5%), flatulence (1.4%), sinusitis (1.2 % vs. 0.5%), and back pain (1.1%). Table 70 presents an overview summary of AEs in the secondary pool by gender and includes duplicate patients and sites #362 and #402.

Table 70: Overview of AEs by Gender in the Secondary Safety Pool

Gender	Number (%) of Patients		
	Placebo QD n (%)	Plecanatide 3 mg QD n (%)	Plecanatide 6 mg QD n (%)
Female	**N=729**	**N=745**	**N=740**
Adverse events	315 (32.9)	439 (38.0)	662 (32.8)
Serious Adverse Events	16 (1.7)	17 (1.5)	25 (1.2)
AEs leading to discontinuation	27 (2.8)	61 (5.3)	119 (5.9)
GI AEs	41 (4.4%)	83 (8.8%)	83 (8.95%)
GI SAEs	0	0	1 (0.11%)
Male	**N=195**	**N=196**	**N=186**
Adverse events	50 (22.3)	80 (30.3)	116 (25.2)
Serious Adverse Events	2 (0.9)	7 (2.7)	6 (1.3)
AEs leading to discontinuation	3 (1.3)	5 (1.9)	22 (4.8)
GI AEs	9 (1.0)	14 (1.5)	12 (1.3)
GI SAEs	0	1 (0.11)	0

Source: Reviewer's Table, Adapted from ISS table 14.3.1.1.2.2.2

Age

Consistent with the primary safety pool, most (89.6%) of the patients in the secondary safety pool were in the subgroup aged <65 years. In the secondary safety pool, including duplicate patients

and sites #362 and #402, the incidence of AEs in the combined plecanatide group was 33.5% in patients aged <65 years and 41.6% in patients aged ≥65 years. The two age subgroups of the combined plecanatide group showed generally similar incidences of AEs considered related to study drug (9.2% for <65 years; 12.1% for ≥65 years), severe AEs (2.7% for <65 years; 4.8% for ≥65 years), and AEs leading to discontinuation of study drug (4.9% for <65 years; 8.6% for ≥65 years).

In regards to the occurrence of specific AEs, the incidence of upper respiratory tract infection was higher in plecanatide patients aged ≥65 years than in plecanatide patients <65 years (3.2% versus 0.8% for primary pool; 3.7% versus 1.5% for secondary pool), whereas the incidence of nausea was higher in plecanatide patients aged <65 years than plecanatide patients aged ≥65 years (1.1% versus 0 for primary pool; 1.8% versus 0.7% for secondary pool).

Race and BMI

In the primary and secondary safety pools, overall, AE rates were similar when analyzed across racial group (white vs. non-white) and BMI groups. SAE rates and rates of discontinuation were also similar.

Reviewer comment: *This reviewer finds that some subgroup differences in AE incidence were observed in both safety pools, however the differences were seen similarly across all treatment groups. These numbers are comparable the AE rates seen in the primary safety pool with the removal of duplicate patients and sites #362 and #402. There appears to be a higher incidence in GI AEs and discontinuation due to AEs in females versus males, in all treatment arms including placebo. There were a slightly higher rate of AEs experienced in females than males, this included AEs of nausea and abdominal distension that were higher in female plecanatide patients than male plecanatide patients (1.1% versus 0.5% for nausea in primary pool; 1.9% versus 0.8% for nausea secondary pool; 1.1% versus 0.5% for abdominal distension in primary pool; 1.6% versus 0.5% for abdominal distension in secondary pool).*

For age, there were higher numbers of patients reporting AEs, SAEs and those discontinuations due to AEs in patients in the older age group, in comparison to the < 65 years old age group. There were no obvious difference of note between the frequency and types of AEs that were reported between race categories. However, comparisons of AE incidence by demographic subgroup were generally limited by low numbers of patients reporting a particular type of event within a particular treatment group and subgroup.

8.7. Specific Safety Studies/Clinical Trials

Not-applicable

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Human carcinogenicity studies were not performed at the time of the NDA submission. Subsequently, nonclinical carcinogenicity studies have been performed which have showed no tumor development. Please see the non-clinical review by Eddie NG, PhD for further details.

8.8.2. Human Reproduction and Pregnancy

Studies of plecanatide in pregnancy and lactating women were not conducted for in the plecanatide development program. Pregnancy and lactating women were excluded from enrollment in the clinical development program. Women of childbearing potential were required to use an effective method of contraception during study participation. All women who became pregnant due in a trial were immediately discontinued form clinical trial presentation and were followed through to the outcome of their pregnancy, when possible.

Twenty pregnancies were reported during the plecanatide clinical development program (including studies that were not pooled for the safety analysis). Four of the pregnancies occurred in Study SP304203-00; two of the patients were never randomized so the events were not captured as treatment-emergent AEs in the pooled ISS analyses. Four pregnancies occurred in Study SP304203-03; eight have occurred in Study SP304203-01 (status of one other pregnancy is unknown since the patient was lost to follow-up; and 4 occurred in Study SP304-20210. The four pregnancies in Study SP304-20210 were not captured as AEs according to protocol. Pregnancies were collected as an independent category. Studies SP304203-00, SP304203-03, and SP304203-01 also did not consider pregnancy as an AE.

In the pregnancy section of the proposed label there is discussion that in animal development studies, no effects on embryo-fetal development were observed with the oral administration of plecanatide in mice and rabbits during organogenesis at doses much higher than the maximum recommended human dose. This section states (b) (4)

In the lactation section of label, nursing and lactation will be addressed in the following way:
(b) (4)

(b) (4)

Table 71: Summary of Non-Serious and Serious Pregnancy Events- Secondary Safety Pool

	Placebo N=870	Plecanatide 3 mg QD N=863	Plecanatide 6 mg QD N=868
Non-Serious Pregnancy [a]	4	4	7
Spontaneous Abortion	2	1	1
Total	6	5	8

Source: Sponsor's Table from June 29, 2016 cover letter

a. Patient carried pregnancy to term and delivered a healthy baby (includes "4" cases where outcome is not known).

Reviewer comment: The data from the unplanned pregnancies during the plecanatide clinical development does not suggest a signal for teratogenicity. Although the number of pregnancies were low and the study was stopped once pregnancy was identified, it does not appear that plecanatide treatment in contributing to the rate spontaneous abortions that higher than expected from background, population rates. The two spontaneous abortions in women receiving plecanatide were not attributed to the study drug. At this time, DPMH does not recommend any additional studies related to the potential impact of plecanatide during pregnancy. However, a milk only lactation study will be required as a PMR. Please refer to DPMH review by Dr. Christos Mastroyanni, for further details.

8.8.3. Pediatrics and Assessment of Effects on Growth

Plecanatide has not been evaluated in patients younger than 18 years. In nonclinical studies, deaths occurred within 24 hours in young juvenile mice (1- to 2-week-old mice) following administration of 1 or 2 oral doses of plecanatide, due to dehydration. Therefore, the use of plecanatide is contraindicated in children up to 6 years of age and should be avoided in persons aged 6 through 17 years. Although no deaths were observed in older juvenile mice (Day 21 or older), the recommendation is based on the observed deaths in young juvenile mice and lack of clinical efficacy and safety data in pediatric patients.

Per the sponsor, plecanatide would be contraindicated <6 years of age. In the iPSP approved on February 5, 2015, the sponsor requested a Waiver of Pediatric Study for pediatric patients from birth to (b) (4) and a Deferral of Pediatric Study for patients of

the following age groups: [redacted] (b) (4) . Please see Table 72 for a comparison of recommended plecanatide pediatric study plans in comparison to the current linaclotide pediatric study plans. Please see the PMR Section 13 for the proposed listed studies, study numbers, and timeline. These studies are subject to change based on the PeRC recommendations and the division's discussion with the sponsor.

Table 72: Plecanatide Proposed Pediatric Study Plan vs. Linaclotide Pediatric Plan

Linaclotide iPSP/WR (WR issued 2016)	Linaclotide Pediatric Plan Age Cohorts	Plecanatide agreed iPSP (agreed in Feb 2015)	Pediatric Plan Recommended During NDA Review and from PeRC meeting (Sept. 29th, 2016)
Waiver – due to safety concerns	0 to (b) (4)	(b) (4)	Waiver for ages 0 to < 2 years
Deferral – until completion of biopsy study to characterize GC-C mRNA expression in pediatric patients AND completion of clinical studies in 6 – 17 years olds	2 to 5 years Will not be performed until GC-C receptor biopsy study is completed in patients age 0-6 years		Deferral for ages 2 to <6 years, until completion of the older age group cohorts and evaluation of results from a GC-C receptor biopsy study in pediatric patients
Deferral – studies ongoing	6 to 17 years (stratified by age group)		Deferral of the dose-finding study of the patients ages 6 years to <12 years of age, until the completion of the 12 to < 18 years of age dose-finding study
			Deferral of the confirmatory efficacy studies for ages 6 to <18 years
Labeling:	Contraindicated in patients < 6 years	Contraindicated in patients < 6 years	Contraindicated in patients < 6 years

Source: Reviewer's Table, based on input from DPMH, the Linaclotide Written Request (WR) issued April 2016and the Plecanatide iPSP dated February 5, 2015. This plan to pending change based on further discussions with the sponsor.

Reviewer comment: The sponsor's waiver and deferral request do not appear appropriate to this reviewer given the nonclinical study data and the sponsor's stated contraindication of plecanatide < 6 years of age. Although the sponsor's initial

Pediatric Study Plan was presented to the Pediatric Research Committee (PeRC) and agreed upon with applicant in February 2015, this review team finds that this plan needs to be revised. In consultation with DPMH and the PeRC (meeting on September 29, 2016), the following changes are proposed:

Per the committee's recommendations, a change in the partial waiver would be expanded from (b) (4) *to < 2 years of age, due to the safety concerns based on the non-clinical, juvenile mice data regarding death due to diarrhea-related dehydration.*

Additionally, deferrals would be provided for the plecanatide studies in pediatric patients from 2 to <18 years of age. PeRC recommended that DGIEP ask the sponsor to revise their studies to include patients from 6 to <12 years of age and 12- (b) (4) *years of age in the same studies. The committee suggest that the sponsor should create fewer studies, since there are currently 3 separate dose-ranging and confirmatory efficacy planned studies. The goal would be to encourage earlier completion of trials in older children and subsequent earlier completion of the pediatric study plan, which extends to 2026 at this time.*

The pediatric studies are suggested to be conducted in a sequential manner, beginning with a phase 2, dose-finding study in adolescents 12 to < 18 years of age (study #1). No deferral would be needed for the start of this study. Subsequently, after the conclusion of study #1 and the evaluation of the results, the dose-finding study (study #3) in younger pediatric patients from 6 to 12 years could start earlier than originally planned. Accordingly, it is recommended by the PeRC committee that the phase 3, confirmatory studies (#2 and #4) for ages 6 to < 12 years of age and 12 to <18 years of age are combined to expedite the pediatric study schedule. It is suggested that a step-down approach is used to enroll the patients based on age. Accordingly, the timeline for the confirmatory studies (#5 and #6) for these two age groups are recommended to have an earlier start time point, after the dose-finding studies are performed. The timing and age cohorts of these study plans may change upon further discussion with the sponsor.

Currently, plecanatide will be contraindicated in patients <6 years of age. It is planned that studies in the 2 to <6 years of age group would be performed once the safety and efficacy results of the older age cohorts are assessed and the colonic biopsy results regarding the GC-C receptor ontogeny are evaluated for safety and potential dosing.

Please see the suggestions in the table below and the review by Carolyn Yancey, MD of DPMH for further information.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no evidence of withdrawal or rebound potential with plecanatide during the clinical development program.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience with this drug because it is not approved at the time of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

Per the sponsor, Based on the safety data for the plecanatide clinical development program, there is an acceptable risk associated with the treatment of plecanatide in adults with CIC. No formal postmarketing Risk Evaluation and Mitigation Strategy (REMS) is required for plecanatide.

Reviewer comment: Based on the safety findings of the NDA submission from the phase 2 and 3 studies of the plecanatide development program, this reviewer expects that diarrhea and abdominal pain-related symptoms will be the most salient AEs that are reported in the post-marketing period. This reviewer does not expect a high frequency of severe AEs to be reported, outside of occasional severe diarrhea.

8.10. Additional Safety Issues From Other Disciplines

Immunogenicity of plecanatide remains a potential concern. PMRs will be created to ensure that assays properly evaluate the possibility of anti-plecanatide antibody development. Additionally, DPMH has concerns regarding the current pediatric study plan's waiver and study age-cohorts. A revised pediatric study plan will be presented to PeRC at the time of this review's completion.

8.11. Integrated Assessment of Safety

Over 3833 patients were exposed to multiple doses of plecanatide during the clinical development program. For the 3mg and the 6mg plecanatide doses, 886 patients were exposed to 6 months of treatment. Additionally, 595 patients were exposed to 12 months of the 3mg and the 6mg plecanatide treatments. Overall, plecanatide was generally well tolerated in during the drug development program.

When removing duplicate patients and those from sites #362 and #402 from the primary safety pool, the overall incidence rates for AEs were comparable across the 3 mg and 6 mg plecanatide treatment groups versus the placebo group (31.7%, 32.5%, and 29.3%, respectively). The safety results in the secondary pool were consistent with those for the primary pool. There were no deaths attributed to plecanatide treatment in the plecanatide developmental program and the most common AEs reported were GI disorders. The incidence of SAEs in the 3mg and 6 mg plecanatide groups were low and comparable to the placebo group (1.5%, 1.0% and 1.3%, respectively). There were SAEs associated with elevations with hepatic enzymes, which are probably not drug-related and were determined by the sponsor to be associated with alcohol intake, concomitant medications, or comorbid conditions such as gall bladder disease. No cases met Hy's law criteria. However, given the slightly higher rate of SAEs, AEs, and laboratory results of elevated hepatic enzymes in patients who were treated with plecanatide versus placebo, the risk of elevated hepatic enzymes should be included in the label.

Additionally, when removing duplicate patients and those from sites #362 and #402 from the primary safety pool, the most frequently reported study-drug-related AE in the combined plecanatide group was diarrhea (5.0%) in comparison to the placebo group (1.3%). There was a slightly greater incidence of severe diarrhea reported in the 3mg and 6 mg plecanatide groups than in the placebo group (0.3%, 1.3% versus 0.3%, respectively). The most frequently reported severe AEs in the in the 3mg and 6 mg plecanatide groups were diarrhea (0.6% and 1.3%, respectively) and abdominal pain (0.3% for both doses). Low incidences of AEs leading to discontinuation of study drug were reported in the 3mg and 6 mg plecanatide and the placebo groups: 4.4%, 4.8%, and 2.3%, respectively, and for severe AEs: 1.4%, 1.0%, and 0.7%, respectively. The most frequently reported events leading to discontinuation reported in the 3mg and 6 mg plecanatide groups were diarrhea (2.1% and 2.0%) and abdominal pain (0.3% and 0.5%).

In general, in the primary safety pool, there was an increased risk of AEs associated with diarrhea, a combination of six combined abdominal pain-related symptoms, and sinusitis in the plecanatide groups versus the placebo. These AEs appeared early in the course of treatment and the frequency of AEs decreased over time after the first 4 weeks of treatment. The analyses showed no trends to suggest an increase in the incidence of any of the most frequently reported preferred terms of AEs over time. Treatment with plecanatide was not associated with any

clinically meaningful differences in AE incidence with respect to gender, age, race, or BMI subgroup.

Currently, plecanatide will be contraindicated in pediatric patients < 6 years of age based on the possibility of severe dehydration and its sequelae as seen in the juvenile mice studies. The pediatric development plan may include further investigation into the ontogeny of the GC-C receptors in pediatric patients and a step-wise, age cohort approach which evaluates the efficacy and safety of plecanatide in older pediatric patients before initiating studies in younger patients. The safety in pregnant and lactating women and to their offspring remains to be elucidated. Although theoretical, there are no substantial signs of uroguanylin deficiency syndrome in the secondary pool analysis. Immunogenicity assay for anti-plecanatide need to be further developed and used in to determine the presence of such antibodies in the tests collected in these trials.

In summary, the analyses of safety profiles for both the plecanatide 3 mg and 6 mg doses for the treatment of adult patients with CIC appears acceptable in the analyzed trials. However, patients who received plecanatide 3mg QD experienced less severe diarrhea and discontinuations due to diarrhea symptoms than the plecanatide 6mg QD group. At the Mid-cycle communication, the (b) (4) (b) (4) plecanatide 6mg dose was presented in this review for a comprehensive evaluation of the safety of plecanatide, (b) (4)

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted.

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the Package Insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, updated patient labeling was not yet been finalized. Please refer to the approved label for the final language. Key changes include, although are not limited to, the removal (b) (4) information throughout the label and the alteration of the box warning to include the risk of serious dehydration in pediatric patients.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

No identified safety issues warrant consideration of REMS.

12 Postmarketing Requirements and Commitments

Post-marketing requirements and commitments (PMR and PMCs) were still under discussion at the time this review was completed. Please refer to the Approval Letter for the final PMR/PMC language. The following proposed PMR and PMC were sent to the sponsor in letter on September 23, 2016 from the review team:

3117-1. 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. Submit screening and confirmation assay validation reports and assay SOPs to the FDA.

3117-2. 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 3117-1, will be used. Evaluate the anti-drug antibody (ADA) rates, individual patient titers

and the relationships between ADA status and the drug safety and efficacy. Provide the study report to the FDA.

3117-3. Develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin. Submit assay validation report and assay SOP to the FDA.

3117-4. Use the validated cross reactivity assays developed under PMR 3117-3 to test the ADA positive samples detected under PMR 3117-2. Evaluate the relationships between cross reactivity status and the drug safety and efficacy. Provide the study report to the FDA.

3117-5. Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. Submit assay validation report and assay SOP to the FDA.

3117-6. Use the validated neutralizing antibody assay developed under PMR 3117-5 to test the anti-plecanatide antibody positive samples detected under PMR 3117-2. Evaluate the relationships between neutralizing antibody status and the drug safety and efficacy. Provide the study report to the FDA.

3117-7. A milk-only lactation trial in lactating women receiving plecanatide therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Lactation subsection of the labeling.

3117-8. A study to characterize GC-C mRNA expression in duodenal and colonic mucosal biopsies obtained from children ages 0 to 6 years of age.

PREA PMRs

3117-9. Study 1: (b) (4) Dose-Ranging Study to Evaluate the Safety and Effectiveness of Plecanatide in Pediatric Subjects (Aged 12 years to (b) (4) years) With CIC (b) (4)

(b) (4)

3117-11. Study 3: (b) (4) Dose Ranging to Evaluate the Safety and Effectiveness of Plecanatide in Pediatric Subject (Aged 6 years to <12 years) With CIC (b) (4)

3117-12. Study 4: A Randomized, Double-Blind Study to Confirm the Safety and Effectiveness of Plecanatide in Pediatric Subjects (Aged 6 years to (b) (4) years) With CIC (b) (4)

3117-13. Study 5: (b) (4) Dose Ranging to Evaluate the Safety and Effectiveness of Plecanatide in Pediatric Subject (Aged 2 years to <6 years) With CIC (b) (4)

3117-14. Study 6: A Randomized, Double-Blind Study to Confirm the Safety and Effectiveness of Plecanatide in Pediatric Subjects (Aged 2 years to <6 years) With CIC (b) (4)

3117-15. Study 7: (b) (4) Long Term Safety Study in Children 2 years to (b) (4) years of age With CIC (b) (4) who have completed a confirmatory efficacy and safety study with Plecanatide

13 Appendices

13.1. References - Refer to footnotes

13.2. Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively.

Table 73: Covered Clinical Study (Name and/or Number): SP304203-00 and SP304203-03

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: SP304203-00: 164 investigators; SP304203-03: 162 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in S Sponsor of covered study: Synergy Pharmaceuticals		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Appendix A

Table 74: Description of Clinical Safety Studies

Study No. No. Centers [1] Country Last Patient Completed	Study Design and Population	Test Product and Comparator Dosage Rescue Medication	Duration of Dosing Duration of Follow-up	Safety Assessments And Population	Key Demographic Characteristics
Phase 3 Efficacy and Safety (Primary Pool [2] & Part of Secondary Pool [3])					
SP304203-00 202/183/164 centers U.S. & CA 23 Apr 2015	Phase 3, randomized, DB, PBO-ctrl study evaluating safety & efficacy of plecanatide in adults with CIC	Plecanatide 3.0 or 6.0 mg tab or PBO tab Once daily orally Rescue med: bisacodyl	12 wk of dosing Follow-up 2 wk after last dose	Monitoring of AEs, clinical labs, vital signs, ECGs, physical exams, antibodies to plecanatide Safety population – 1389 patients: 931 plecanatide (474 at 3 mg & 457 at 6 mg; 770 for 12 wk) 458 PBO	Females: 80.7% plecanatide: 81.3%; PBO: 79.5% Median age: 46.0 yr plecanatide: 45.0 yr; PBO: 46.0 yr Pred. race: white (68.5%) plecanatide: 67.5%; PBO: 70.7% Median BMI: 27.67 kg/m^2 plecanatide: 27.63 kg/m^2; PBO: 27.85 kg/m^2

SP304203-03 185/180/162 centers U.S. 13 May 2015	Phase 3, randomized, DB, PBO-ctrl study evaluating safety & efficacy of plecanatide in adults with CIC	Plecanatide 3.0 or 6.0 mg tab or PBO tab Once daily orally Rescue med: bisacodyl	12 wk of dosing Follow-up 2 wk after last dose	Monitoring of AEs, clinical labs, vital signs, ECGs, physical exams, antibodies to plecanatide Safety population – 1402 patients: 936 plecanatide (467 at 3 mg, 469 at 6 mg; 803 for 12 wk) 466 PBO	Females: 78.0% plecanatide: 77.8%; PBO: 78.3% Median age: 45.0 yr plecanatide: 46.0 yr; PBO: 44.5 yr Pred. race: white (74.5%) plecanatide: 74.5%; PBO: 74.5% Median BMI: 27.77 kg/m^2 plecanatide: 28.08 kg/m^2; PBO: 27.36 kg/m^2
Phase 3 Long-term Safety (Part of Secondary Pool [3])					
SP304203-01 228/217/214 centers U.S. 9/9/9 centers Canada	Phase 3, open-label, long-term study evaluating safety & tolerability of plecanatide in adults with CIC	Plecanatide 3.0 or 6.0 mg tab Once daily orally Rescue med: bisacodyl	Up to 2 years of dosing	Monitoring of AEs, clinical labs, vital signs, ECGs, physical exams, antibodies to plecanatide Safety population – 1782 plecanatide (230 at 3 mg & 1552 at 6 mg; 446 for >52 wk)	NA [4]
Phase 2 (Part of Secondary Pool [3])					
SP304-20210 121/115/113 centers U.S. 06 Dec 2012	Phase 2b, randomized, DB, PBO-ctrl, dose-ranging study evaluating safety & efficacy of plecanatide in adults with CIC	Plecanatide 0.3, 1.0, or 3.0 mg cap or PBO cap Once daily orally Rescue med: bisacodyl	12 wk of dosing Follow-up 2 wk after last dose	Monitoring of AEs, clinical labs, vital signs, ECGs, physical exams Safety population – 948 patients: 712 plecanatide (567 for 12 wk) 236 PBO	Females: 86.4% plecanatide: 85.7%; PBO: 88.6% Median age: plecanatide: 48.0 yr; PBO: 46.5 yr Pred. race: White (72.5%) plecanatide: 72.5%; PBO: 72.5% Median BMI: plecanatide: 27.39 kg/m^2; PBO: 26.81 kg/m^2

Study No. No. Centers [1] Country Last Patient Completed	Study Design and Population	Test Product and Comparator Dosage Rescue Medication	Duration of Dosing Duration of Follow-up	Safety Assessments and Population	Key Demographic Characteristics
SP304101-09 1/1/1 center U.S. 23 Apr 2013	Phase 1, single-blind, PBO-ctrl, crossover, randomized (8:2 & to treatment sequence and then to active drug or PBO), single-dose study evaluating effect of food on PD, PK, safety, & tolerability of plecanatide in healthy adults	Plecanatide tab or PBO tab Single oral 9-mg dose under 3 meal conditions: fasted fed HFHC meal fed LFLC meal No rescue med	3 days of dosing (total) with 7-day washout between treatments Follow-up 7 & 14 days after last dose	Monitoring of AEs, clinical labs, vital signs, ECGs, physical exams, antibodies to plecanatide Safety population – 30 subjects: 24 plecanatide 6 PBO	Males: 76.7% plecanatide: 79.2%; PBO: 66.7% Median age: 43.5 yr plecanatide: 43.5 yr; PBO: 40.5 yr Pred. race: white (90.0%) plecanatide: 91.7%; PBO: 83.3% Median BMI: 28.35 kg/m^2 plecanatide: 27.90 kg/m^2; PBO: 28.90 kg/m^2

AE = adverse event; BMI = body mass index; CA = Canada; cap = capsule; CIC = chronic idiopathic constipation; con = concomitant; ctrl = controlled; DB = double-blind; ECG = electrocardiogram; exams = examinations; HFHC = high-fat, high-calorie; IBS-C = irritable bowel syndrome with constipation; labs = laboratory tests; LFLC = low-fat, low-calorie; med = medication; NA = not applicable; PBO = placebo; PBS = phosphate buffered saline; PD = pharmacodynamic(s); PK = pharmacokinetic(s); pred. = predominant; tab = tablet; U.S. = United States

[1] Number of centers initiated/number of centers activated (screened at least 1 patient or subject)/number of centers that randomized at least 1 patient or subject (or treated at least 1 patient in Study SP304203-01).

[2] The primary pool consisted of the double-blind, placebo-controlled, phase 3 Studies SP304203-00 and SP304203-03 (Section 1.5.1).

[3] The secondary pool consisted of the studies in the primary pool (SP304203-00 and SP304203-03), phase 3 Study SP304203-01 (interim data), phase 2b study SP-304-20210, and phase 2 Study SP-304201-09 (Section 1.5.1).

[4] By-study interim safety data from Study SP304203-01 are presented only as pooled data in the secondary study pool. Source: Individual study protocols and clinical study reports; Post-text Tables 14.1.0 and 14.1.2.4.2

Table 75: Study Administrative Structure - Provided by the Sponsor

Role	Contact Information
Sponsor:	Synergy Pharmaceuticals Inc. 420 Lexington Avenue, Suite 2012 New York, NY 10170 P: +1 212-297-0020
Clinical Research Organizations/ Project Management:	(b) (4)
Medical Monitor:	
Data Management:	
SAE Reporting:	
Biostatistics:	
Central Clinical Laboratory:	
Randomization and Trial Supply Management	
Drug Manufacturer:	
Drug Packaging and Distribution:	
Electronic Hand Held Devices and Tablets for Patient Diaries and Questionnaires (ePRO):	

Electronic Hand-Held Device Questions

Daily Bowel Movement Diary

_ Confirm you would like to report a Bowel Movement that occurred today. (Yes / No)
_ Please record the time that this Bowel Movement occurred today.
_ Did you feel like you completely emptied your bowels during this Bowel Movement? (Yes / No)
_ Select the picture most resembling your stool. [Bristol Stool Form Scale graphic shows on screen]
_ Please remember to tell the [device name] each time you have a Bowel Movement.
_ Please remember that even if you enter bowel movements or rescue medication use during the day you still need to complete Daily Symptom Diary in the evening every day.

Rescue Medication Usage

_ Confirm you are ready to take Dulcolax® now. (Yes / No / Already Taken)
_ On the following screens, please review the Rescue Medication (Dulcolax®) entries you have made in the [device name] so far today.
_ You recorded taking Dulcolax® at the following time(s) today: [DAY] [Time] [Number of pills]
_ Do you still need to record a time that you took Dulcolax® today? (Yes / No)
_ Please record the time that you took your Dulcolax® today.
_ Enter the number of pills you took at this time.
_ Please remember to tell the [device name] each time you take your Dulcolax®.

Daily Symptom Diary

The patient will be asked to rate their symptoms using their EHD.
This questionnaire should be answered each day during the Daily Symptom Diary completed in the evening. There is not an option to enter data from a previous day in this study.
_ The Daily Symptom Diary begins now…
_ You will enter your response on a scale of 0 to 4, where 0 is none , 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe.
_ 1. Abdominal Bloating. For today, rate your abdominal bloating at its worst on a scale of 0 to 4.
_ 2. Abdominal Discomfort. For today, rate your abdominal discomfort at its worst on a scale of 0 to 4.
_ 3. Abdominal Pain. For today, rate your abdominal pain at its worst on a scale of 0 to 4.
_ Today, did you have a bowel movement? (Yes / No)
_ 4. Straining. For today, when you had a bowel movement, rate your straining at its worst on a scale of 0 to 4.

Source: Sponsor's CSR Study -00 and -03.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLEY A HANES
10/12/2016

LAURIE B MULDOWNEY
10/12/2016