CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 202-292
Drug Name:	Crofelemer tablets (125 mg)
Indication(s):	The control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.
Applicant:	Salix Pharmaceuticals, Inc.
Date(s):	Receipt date: 12/5/2011 PDUFA goal date: 9/5/2012
Review Priority:	Priority
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Keywords: NDA review, clinical studies, closed-test procedures, data monitoring committee, exact test, interim analysis, one-sided/two-sided tests

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1 EXECUTIVE SUMMARY

The statistical evidence to support the desired indication for crofelemer, "the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy", is modest. The primary evidence comes from a single study called the ADVENT Trial. Although the difference between the clinical response rates for crofelemer 125 mg (18%) and placebo (8%) is statistically significant at α=0.025 (p-value = 0.01, one-sided) with a one-sided 97.5% confidence interval of [1.2%, ∞], the 10% treatment effect size is not consistent across important study design attributes, including stage of study and study sites. Further, the within group clinical response rate of 18% for crofelemer 125 mg is relatively low.

ADVENT was a two-stage adaptive design study. Subjects who enrolled in Stage I were randomized to one of three crofelemer doses (125 mg, 250 mg, 500 mg) or placebo. Each treatment group had approximately 50 subjects. Based on the results of an interim analysis, the 125 mg dose was selected for further study in Stage II. Therefore, subjects who enrolled in Stage II were randomized to either 125 mg (n=92) or placebo (n=88). All subjects had the option of enrolling in a five month, placebo-free, open-label, follow-up period.

Notably, the treatment effect was not consistent across study stage and was statistically significant for Stage I only, despite a larger sample size in Stage II; see Table 7 and Table 8 of my review. The size of the Stage I treatment effect (18%; p=.0019, one-sided) was larger than the size of the Stage II treatment effect (5%; p=.1690, one-sided). The Applicant explained this difference by noting (1) that crofelemer had a more profound treatment effect in subjects with more clinically significant diarrhea and (2) that the Stage II placebo subjects had more clinically significant diarrhea as assessed by the number of watery stools at baseline than did the Stage I placebo subjects. Therefore, they asserted, the difference was likely due to the imbalance between stages in clinically significant diarrhea among the placebo-treated subjects. My review, however, suggests the imbalance may be due to two placebo-treated subjects who had unusually high baseline values of watery stools. In addition, the point estimate of the treatment effect for subjects with less severe diarrhea was comparable to the point estimate of the treatment effect for subjects with more severe diarrhea.

Further, the treatment effect was not consistent across study sites. The largest study site (n=36) did not show any treatment effect, with only one responder in the crofelemer 125 mg treatment group and only one responder in the placebo treatment group.

Based on the relatively small numbers of clinical responders who entered the placebo-free phase, the results suggest a reasonable number of the crofelemer 125 mg responders maintained their response. Of the crofelemer 125 mg responders (n=22) who entered the placebo-free phase, 14 were responders through every month of the PF phase. However, this result needs to be balanced by the finding that 5 lost their response to treatment by Month 3 of the placebo-free phase.

The Botanical Review Team requested analyses to assess whether the clinical response of crofelemer-treated subjects and crofelemer batch were related. Although the clinical response

rates appear similar across batches, this analysis is simplistic and can not be relied upon to give conclusions that are reliable. An appropriate analysis needs to consider the study design features and the clinical response rates among concurrent placebo controls. For example, one batch was used in Stage II only and not in Stage I. Because this batch was not used in Stage I, we are unable to assess whether difference in the treatment effect size between stages is due to batches or the study design.

The ADVENT trial also illustrates perils that may occur when two-stage adaptive designs are used for Phase 3 studies. If the rules for selecting a dose permitted stopping the study for futility at the interim analysis, the dose selection meeting minutes suggest the interim analysis committee may have recommended stopping the study due to the lack of a meaningful difference in the clinical response rates among the treatment groups. However, the response rates calculated at the interim analysis differed from those used in the final analysis of the study results, resulting in an underestimate by the interim analysis of the difference between the response rates for crofelemer 125 mg and placebo at the interim analysis: 8% at the interim vs. 18% for the final. Two reasons accounted for this difference. First, the consulting statistician who did the interim analysis mistakenly included data from the post-randomization three-day run-in period in his calculation of response rates instead of excluding these days as stipulated in the protocol. Second, the sources of data used to define clinical non-responders differed between the two analyses. At the interim analysis, only the daily diary data were used to determine the use of anti-diarrheal medications and opiates. The final analysis used an additional data source – the electronic case report form. Taken together, these two reasons changed the response rates in a way that increased the treatment effect seen for Stage I. Had a futility rule been in place at the time of the interim analysis, the study may have been stopped needlessly.

2 INTRODUCTION

2.1 Overview

The Applicant is seeking the following indication for crofelemer at a recommended dose of 125 mg twice daily (BID):

> The control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.

Because no approved product is available to treat secretory diarrhea in patients with HIV, a serious condition with an unmet need, this NDA has received a priority review designation.

My review is limited to NP303-101, also know as ADVENT, which is one of the three double-blind, placebo-controlled studies that assessed the safety and efficacy of crofelemer for the desired indication; see Table 1. ADVENT is considered the confirmatory study. One of the other studies was a Phase 3 study (37554-210) and one was a Phase 2 study (37554-209). The medical division is not relying on them for evidence of efficacy, primarily due to the study endpoint used in the studies.

Table 1. Studies contained in the NDA

Study Number	Study Design/Crofelemer Regimen/ Control Regimen	Duration	Subject Population
NP303-101 (ADVENT)	Double-blind, placebo-controlled, 2-stage, adaptive design, phase 3 study • Crofelemer 125 mg BID tablets (n=136)[a] • Crofelemer 250 mg BID tablets (n=54)[a] • Crofelemer 500 mg BID tablets (n=46)[a] • Placebo BID tablets (n=138)[a]	4 weeks of PC treatment; 20 weeks of PF treatment	HIV+ subjects on stable ART with ≥ 1 month history of diarrhea
37554-210	Double-blind, placebo-controlled, phase 3 study • Crofelemer 250 mg QID tablets (n=102) • Crofelemer 500 mg QID tablets (n=100) • Crofelemer 500 mg QID beads (n=100) • Placebo QID (n=98)	6 days of inpatient treatment; 21 days of outpatient treatment	HIV/AIDS subjects on stable treatment regimen for AIDS with ≥ 14 day history of diarrhea
37554-209	Double-blind, placebo-controlled, phase 2 study • Crofelemer 500 mg QID beads (n=43) • Placebo QID (n=42)	4 days of inpatient treatment	HIV/AIDS subjects on stable treatment regimen for AIDS with diarrhea

Abbreviations: HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome; PC = placebo-controlled; PF = placebo-free; BID = twice daily; QID = 4 times daily; and ART = antiretroviral therapy.

a Number of subjects in the PC treatment phase.

Source: Table 1, Clinical Overview of the NDA

Notably, ADVENT incorporated an adaptive design. The study included two stages. Stage I identified the dose that was assessed subsequently in Stage II. The results from both stages were combined using the methodology of Posch et. al., which combines the p-values from each stage by a weighting procedure[1]. The details of the design are discussed in Section 3.2.1.5 of this review.

(b) (4)

(b) (4)

(b) (4)

This observation led to the Phase 2 study (37544-209), which was completed in 1997. In that study, 51 evaluable subjects with HIV-associated diarrhea received either crofelemer or placebo for four days in an inpatient setting. Analyses suggested efficacy for improvements in stool weight and stool frequency.

A Phase 3 study (37544-210) was completed in 1998. In that study, 400 subjects with chronic HIV-associated diarrhea were treated with crofelemer or placebo for 7 days in an inpatient setting. Subjects who responded to treatment were continued in a three-week blinded outpatient phase. Although the treatment effect was not statistically significant, an analysis limited to subjects with watery diarrhea and urgency at baseline showed a statistically significant improvement in stool frequency and weight ($p<0.05$) with treatment. (b) (4)

[1] Posch M, Koenig F, Branson M, Brannath W, Dunger-Baldauf C, Bauer P. Testing and estimation in flexible group sequential designs with adaptive treatment selection. Statistics in Medicine 2005 Dec 30;24(24):3697-714.

Napo (formerly PS Pharmaceuticals and formerly Shaman) met with FDA in 2004 to discuss an additional Phase 3 study. The FDA agreed the proposed concept met the requirements for an additional study. (b) (4)

In 2006, Napo submitted a request for a Special Protocol Assessment of a two-stage adaptive designed clinical study. Although a formal SPA agreement was never reached, numerous communications between Napo and the FDA occurred from 2006 through 2007 regarding the adaptive study design, the primary endpoint, and statistical methodology.

In December 2008, IND 51818 was transferred from Napo to Salix, the current applicant.

In addition to studies of HIV-related diarrhea, crofelemer has been studied for other conditions including diarrhea-predominant IBS, traveler's diarrhea, non-specific diarrhea, and cholera.

2.2 Data Sources

Response to FDA Request for Information, response submitted 2/14/2012, Sequence 003 (contains lot and batch datasets)

Response to FDA Request for Information, response submitted 2/29/2012, Sequence 005

Response to FDA Request for Information, response submitted 3/15/2012, Sequence 006

Response to FDA Request for Information, response submitted 7/2/2012, Sequence 016

Response to FDA Request for Information, response submitted 7/13/2012, Sequence 018

Response to FDA Request for Information, response submitted 8/22/2012, Sequence 024

Response to FDA Request for Information, response submitted 9/12/2012, Sequence 032

Original NDA submission, submission dated 12/06/2011, Sequence 0

ADVENT datasets

Posch M, Koenig F, Branson M, Brannath W, Dunger-Baldauf C, Bauer P. Testing and estimation in flexible group sequential designs with adaptive treatment selection. Statistics in Medicine 2005 Dec 30; 24(24):3697-714.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

A SAS macro, written by the Applicant, was used to calculate the overall p-value for the ADVENT trial. The overall p-value for the statistical test comparing crofelemer 125 mg with placebo was based on combining p-values from Stage I and Stage II of ADVENT. The code for the macro was not submitted with the original NDA and had to be requested during the NDA review; see Appendix 6-1. The macro does not contain internal annotations, which led to a significant amount of review time devoted to interpreting and testing each line of code in order to understand what was being executed.

My review found that the macro was written specifically to accommodate the rank order of the p-values arising from the Stage I pairwise comparisons between treatment and placebo. The macro requires the input of the number of subjects and number of responders for each treatment and stage. Once I understood how the code worked, I was able to reproduce the results for the primary endpoint. Moreover, the 'Response from Applicant to Information requested on March 5, 2012' states the SAS macro is able to reproduce the adjusted overall p-values and adjusted one-sided 97.5% confidence interval shown in the example of Section 6.2 in the Posch et al (2005) publication, thus implying the SAS macro is validated.

Because the definition of the primary endpoint relies heavily on the eDiary data captured by an interactive voice response system and on data entered into electronic case report forms, I asked the Office of Scientific Investigations for the results of their reviews of these data. They believe these two processes yielded reliable data.

3.2 Evaluation of Efficacy

Although the submission contains three, randomized, placebo-controlled studies, my review focuses on the ADVENT trial (NP-303-01), which the medical division has identified as the primary study to support the efficacy of crofelemer:

> Study ADVENT (NP-303-01): "Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Two Stage Study to Assess the Efficacy and Safety of Crofelemer 125mg, 250 mg, and 500 mg Orally Twice Daily for the Treatment of HIV Associated Diarrhea (ADVENT Trial)"

3.2.1 Study Design and Endpoints

This section describes the study objective and design of ADVENT (NP-303-01), the interactive voice response system (IVRS) that was used to capture daily diary information, the definition of the primary endpoint, and the procedures used to implement the adaptation. Later in my review (Section 3.2.4.1), I describe and evaluate the interim analysis results that were used to select the dose that was studied in Stage II.

3.2.1.1 Study objective and study design

The objective of ADVENT is to confirm the therapeutic benefit for crofelemer in the treatment of diarrhea in HIV-positive individuals, and to select the optimal dose for crofelemer in this indication.

To achieve the study's objective, an adaptive design comprising two stages was used. Each stage was double-blind and placebo-controlled. The purpose of Stage I was to select an optimal dose for the treatment of diarrhea in HIV-positive individuals; this dose would be the only dose assessed in Stage II. Subjects participated in either Stage I or Stage II, but not both. The statistical analysis plan called for combining the results from both stages using the methods of Posch et al (2005).[1]

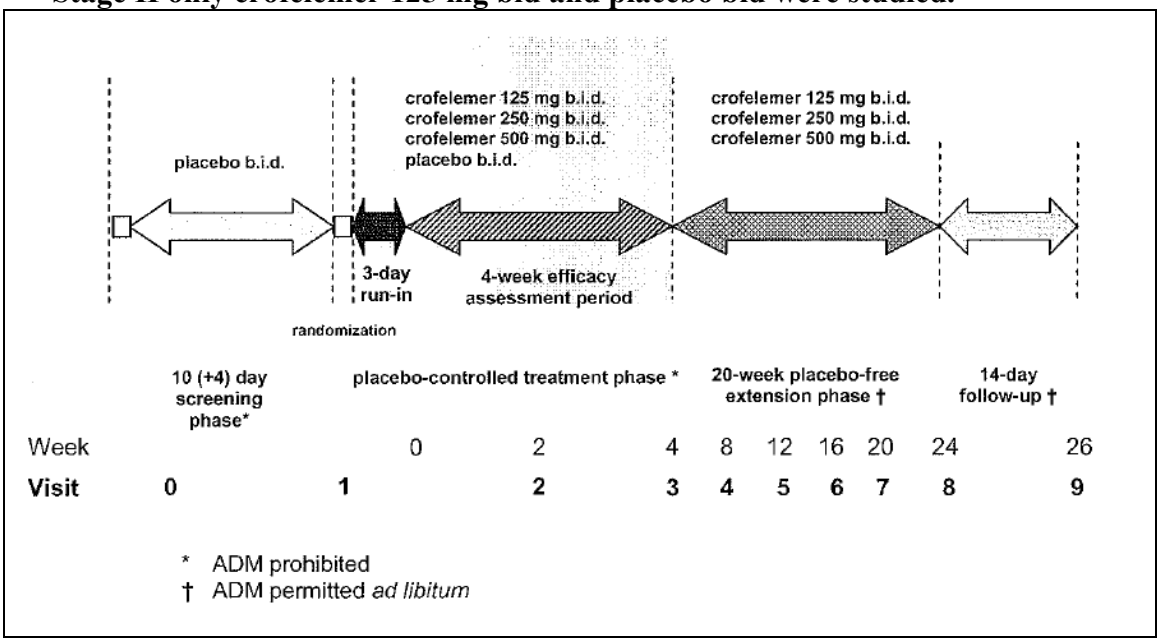
Stage I and Stage II each consisted of (see Figure 1):

- A single-blind, placebo screening phase lasting 10 days,
- Randomization,
- A 31-day, double-blind, placebo-controlled treatment phase consisting of
    - a three-day run-in period and
    - a four-week assessment period,
- A 20-week placebo-free extension phase in which crofelemer-treated subjects remained on their assigned doses, Stage I placebo-treated subjects were re-randomized to one of the three crofelemer doses, and Stage II placebo-treated subjects received crofelemer 125 mg, and
- A 14-day post-dosing telephone call for assessment of adverse events.

Eligible subjects had a confirmed diagnosis of HIV and a history of diarrhea defined as either persistently loose stools despite regular anti-diarrhea medication (ADM) use, or one or more watery bowel movements per day without regular ADM use, of at least one month duration, and for the month prior to screening. Subjects were to be on a stable regimen of antiretroviral therapy for at least four weeks prior to screening and able to stay on the regimen during screening, baseline and the placebo-controlled portion of the study. Subjects with CD4 counts $<100/mm^3$ were excluded from the study. A subject with less than 5 days of efficacy data recorded using an interactive voice response system (IVRS) during the screening phase was not randomized.

With a total of 250 subjects – 125 subjects randomized to each of two treatment groups (125 mg crofelemer and placebo), the power of the study was estimated to range from 71% to over 91% to detect a treatment difference at a one-sided alpha of 0.025 when the underlying response rate of one or more of the crofelemer dose groups exceeds placebo by 20%. The clinical response of 20% is based on an estimated response rate of 55% in crofelemer and 35% in placebo during the four-week efficacy assessment period.

Figure 1. Outline of treatment phases and visits for Stage I and Stage II. In Stage II only crofelemer 125 mg bid and placebo bid were studied.



Source: Figure 1, Clinical Study Protocol for NP303-101 (ADVENT)

3.2.1.2 The Interactive Voice Response System

In both stages, diary entries were recorded daily using an Interactive Voice Response System (IVRS); see Figure 2 and Figure 3. Information entered into the diary during all study phases included bowel movement frequency, consistency, urgency, fecal incontinence, abdominal pain or discomfort, use of anti-diarrhea medication, adherence to study medication and adherence to HIV medication. Additionally, during baseline and the double-blind treatment phase but not the placebo-free extension phase, opiate pain medication use was captured (see Figure 3). Data obtained during the last 7 days of the single-blind screening phase served as baseline for all statistical evaluations.

Figure 2. Information recorded daily during all study phases, using an IVRS

(a) Date (automatic).
(b) Number of watery bowel movements: "Please enter the total number of watery bowel movements you experienced on [weekday]."
(c) Number of loose bowel movements: "Please enter the total number of loose bowel movements you experienced on [weekday]."
(d) Number of formed bowel movements: "Please enter the total number of formed bowel movements you experienced on [weekday]."
(e) Number of hard bowel movements: "Please enter the total number of hard bowel movements you experienced on [weekday]."
(f) Number of very hard bowel movements: "Please enter the total number of very hard bowel movements you experienced on [weekday]."
(g) Presence of urgency: "Did you have to rush to the bathroom for a bowel movement on [weekday]?" (Yes or No)
(h) Presence of fecal incontinence: "Did you leak or pass stool at unwanted times on [weekday]?" (Yes or No)
(i) Abdominal pain or discomfort: "Please rate your level of abdominal pain or discomfort on [weekday]."
    0 = none
    1 = mild
    2 = moderate
    3 = severe
(j) Adherence to study medication: "Did you take all of your study medication on [weekday]?" (Yes or No)
(k) Adherence to ART: "Did you take all of your prescribed HIV medication on [weekday]?" (Yes or No)
(l) Use of anti-diarrhea medication (ADM): "Did you use any anti-diarrhea medication other than study medication on [weekday]?" (Yes or No)

Source: ADVENT Clinical Study Report, Section 9.5.2.1.

Figure 3. Information recorded daily during baseline and the placeb-controlled treatment phase, using an IVRS

(j) Use of prohibited opiate pain medications: "Did you use any opiate pain medications on [weekday] that were not authorized by your study doctor?" (Yes or No)

Source: ADVENT Clinical Study Report, Section 9.5.2.1.

3.2.1.3 Capturing the use of ADM or opiate pain medication

Because the use of ADM or opiate pain medication contributed to the definition of a clinical non-responder, it is important to know how this information was captured and used to define a subject as a clinical responder or clinical non-responder. This information will aid in the understanding and interpretation of the study results. Although ADM and opiate pain medication use were captured both by the IVRS and the electronic case report form (eCRF), the interim analysis relied solely on the IVRS while the final analysis used both sources of data.

If a subject recorded ADM or opiate use on an IVRS entry, the IVRS automatically notified the investigator[2]. The investigator was instructed to discuss the use of this ADM with the subject. Additionally, at each clinic visit, the study staff reviewed IVRS entries with the subject and discussed entries that indicated ADM use.

Prohibited medications were also captured on the 'Prior and Concomitant Medications' eCRF[3]. At each clinic visit, study staff reviewed the use of concomitant medications with the subject, and discussed any prohibited medication use since the previous study visit. The study staff entered this information onto the eCRF.

Edit checks were run to reconcile prohibited medications reported on the eCRF with information reported in the IVRS after the interim analysis and before the database lock. When a prohibited medication was reported as being taken either with the IVRS or on the concomitant medication page of the eCRF, the medication was considered taken. Thus, data from both the eCRF and IVRS were used in the final efficacy analyses, which were performed by Salix.

3.2.1.4 Definition of primary endpoint

The primary endpoint was clinical response, and included contributions from data captured by both the IVRS and eCRF.

A subject was classified as a *responder* if

- The subject reported two or less watery bowel movements per week during at least two of the four weeks of the efficacy assessment period of the placebo-controlled treatment phase.

A subject was classified as a *non-responder* if

- The subject used an anti-diarrhea medication or opiate pain medication, including any combination of ADM or opiate pain medication, for greater then 3 days (consecutive or non-consecutive) during the 4-week efficacy assessment period.
- The subject discontinued before Visit 3 during the 4-week efficacy assessment period.

Note the definition of clinical response excludes results from the three-day run-in immediately following randomization. Moreover, although the protocol does not explicitly define 'discontinue', which can mean either discontinuation from study treatment or discontinuation from treatment, Section 4.1.4 of the protocol implies 'discontinuation' means stopping study participation during the 4-week efficacy assessment period.

[2] See Section 5.9.1 of the study protocol; and the Applicant's Response to an Information Request dated 2/28/2012, Sequence 005.
[3] See the Applicant's Response to an Information Request dated 2/28/2012, Sequence 005.

3.2.1.5 Description of adaptation procedures

In Stage I, the protocol called for a total of 200 subjects, or approximately 50 subjects per group, to be randomized in a 1:1:1:1 ratio to four treatment groups:

- Placebo bid
- 125 mg crofelemer bid
- 250 mg crofelemer bid
- 500 mg crofelemer bid

At the end of the 31-day double-blind placebo-controlled treatment phase, subjects on crofelemer were to remain on their assigned dose; placebo-treated subjects were to be re-randomized to one of the three crofelemer doses. The subjects enrolled in the placebo-free extension phase were followed for 20 weeks.

After the final subject completed the placebo-controlled treatment phase of Stage I, an interim analysis was conducted and, based on these results, an independent analysis committee selected 125 mg crofelemer bid for study in Stage II. The interim analysis was not to be used to adjust the sample size or to stop the study early for efficacy. Section 3.2.4.1 of my review describes the results of the interim analysis and dose selection procedure.

In Stage II, the protocol called for a total of 150 subjects, or approximately 75 subjects per group, to be randomized in a 1:1 ratio to placebo or the crofelemer dose selected at the end of Stage I:

- Placebo bid
- 125 mg crofelemer bid

At the end of the placebo-controlled treatment phase of Stage II, all subjects were to receive 125 mg crofelemer bid during the 20 week placebo-free extension period.

The protocol indicates the following steps were to be taken to prevent the results of the analysis of the data from Stage I from introducing bias into the results from Stage II:

Figure 4. Steps taken to prevent the knowledge of the Stage I interim analysis results from influencing the Stage II conduct and results

- The interim analysis will be conducted by a Consulting Statistician (CS) who is not a Salix employee. The CS is not a Salix employee and has no direct relationship to the CRO handling the site monitoring and data management. All analyses will be prepared by the CS and entered into an Interim Analysis Report.
- The randomization code will be prepared by the CS and stored on a computer that Salix cannot access.
- The CS will conduct the interim analysis using statistical software files that neither Salix nor the CRO monitoring the trial can access.
- The interim analysis will examine only the primary efficacy variable in the ITT population and AE and SAE rates; it will not reveal results by investigative site or patient.
- The electronic copy of the Interim Analysis Report will be written and stored on a computer that Salix cannot access.
- A paper copy of the Interim Analysis Report will be provided to an independent committee (Interim Analysis Committee). The members of the committee will be knowledgeable on crofelemer and the ADVENT protocol. None of the Interim Analysis Committee members will bear any responsibility for study conduct. The Interim Analysis Committee will select the dose of crofelemer to be employed in Stage II and share that decision only with those personnel required to prepare and ship the doses for Stage II.

Source: Section 9.1.3 of the protocol

The protocol states the selection of the dose of crofelemer to be studied in Stage II would be made by the Interim Analysis Committee (IAC) based on the following criteria:

Figure 5. Criteria used by the Interim Analysis Committee to select the optimal dose of crofelemer

1. The primary efficacy variable in the ITT population, concomitant with AE and SAE rates.

2. Assuming there are no safety issues, the crofelemer dose selected for Stage II will be one for whom the primary efficacy variable in the ITT population is at least 2.0% greater than the other crofelemer treatments. If there are safety issues, the decision as to dose selection is too complex to pre-specify.

3. If 2 or 3 treatment groups' percents are less than 2% of each other, and there are no safety issues, the lowest of these doses will be selected for Stage II.

Source: Section 9.1.3 of the protocol

In addition, the protocol also indicates the Interim Analysis Committee would examine unblinded safety information in order to help select the optimal dose of crofelemer and to identify any safety signals.

The criteria for selecting the dose were to be documented in the Dose Selection Report, and the paper copies of the Interim Analysis Report and Dose Selection Report were to be sealed and stored by the CRO handling the data analysis. The plan was to unblind the reports when the clinical study report was written; the Interim Analysis Report and Dose Selection Report would be provided in the clinical study report.

The IAC comprised a Consulting Statistician (non-voting) and four independent, external consultants knowledgeable of the NP303-101 program:

- (b) (4)

The statistician (b) (4) was responsible for compiling the efficacy and safety tables, and listings for the Interim Analysis Report.

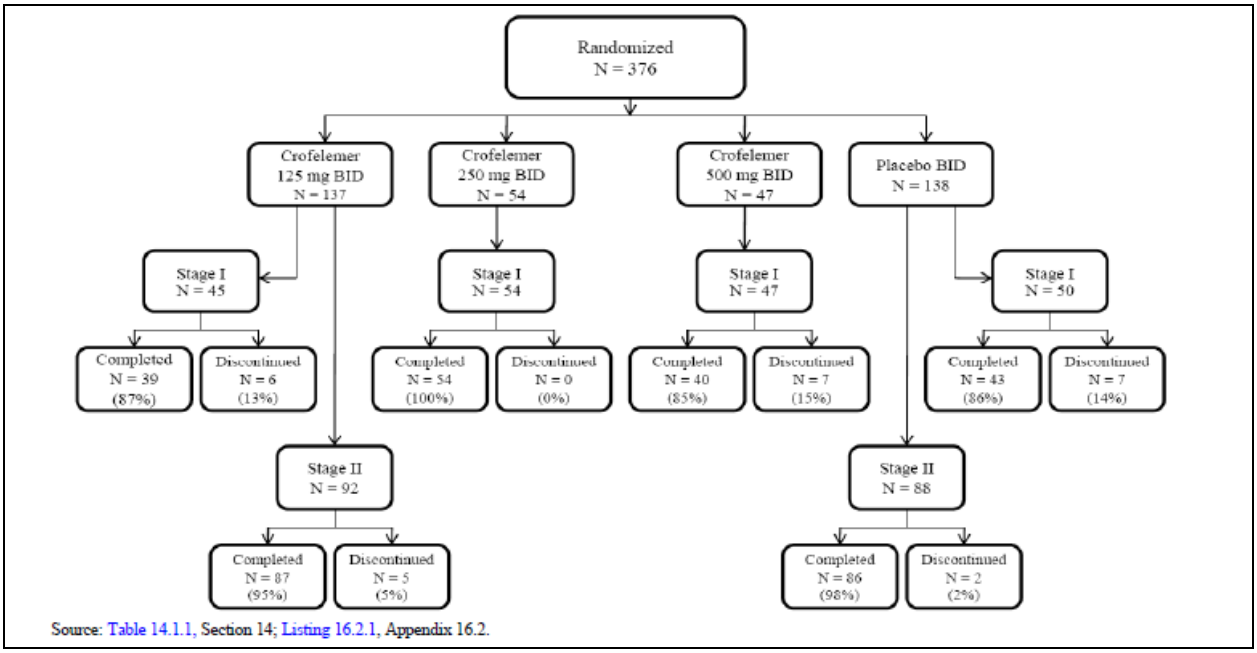
In order to conduct the interim analysis, the IVRS vendor provided SAS files containing the data needed to perform the interim analysis. The IVRS vendor provided the randomization codes separately by secure mail. The statistician prepared an electronic copy of the interim analysis report using files that, according to the protocol, could not be accessed by Salix, Napo or the delegated study personnel.

The electronic copy of the Interim Analysis Report and associated data were to be stored on a secure server at (b) (4) which is owned by (b) (4) Paper copies were to be provided to the IAC members.

3.2.2 Subject Disposition, Demographic and Baseline Characteristics

Figure 6 depicts the number of subjects who were randomized to each of the four treatment groups, both overall and by stage. The figure also shows the number of subjects who completed the study. For the crofelemer 125 mg bid and placebo treatment groups, the completion rates among subjects enrolled during Stage I were around 85% and increased to over 95% among subjects enrolled during Stage II.

Figure 6. A flow diagram that shows for Stage I and Stage II the number of subjects who were randomized to each treatment arm, the number who completed the placebo-controlled treatment phase and the number who discontinued.



Source: Figure 5, Clinical Study Report for ADVENT

Across both Stage I and Stage II combined, the discontinuation rates were 8% for crofelemer 125 mg bid and 7% for placebo bid; see Table 2. The reasons for discontinuation did not appear to differ among the two treatment groups.

Table 2. Reasons for discontinuation during the placebo-controlled treatment phase and during the placebo-free extension phase; Stage I and Stage II pooled together.

	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo BID n (%)
Placebo- Controlled Treatment Phase				
Subjects Randomized (N)	**137**	**54**	**47**	**138**
Subjects Treated	136 (99)	54 (100)	46 (98)	138 (100)
Completed	126 (92)	54 (100)	40 (85)	129 (94)
Discontinued	11 (8)	0	7 (15)	9 (7)
Primary reason for discontinuation				
Withdrawal of consent	3 (2)	0	5 (11)	1 (1)
Loss to follow-up	4 (3)	0	2 (4)	0
Adverse event[a]	0	0	0	3 (2)
Exacerbation of diarrhea	0	0	0	2 (1)
Noncompliance with IVRS	1 (1)	0	0	1 (1)
Noncomplicance with study drug	2 (2)	0	0	0
Repeated use of ADM or opiates	0	0	0	1 (1)
Other[b]	1 (1)	0	0	1 (1)
Placebo-Free Extension Phase				
Entered Placebo-Free Extension (N)	**220**	**67**	**50**	
Completed	185 (84)	49 (73)	40 (80)	
Discontinued	35 (16)	18 (27)	10 (20)	
Primary reason for discontinuation				
Withdrawal of consent	15 (7)	6 (9)	1 (2)	
Loss to follow-up	5 (2)	4 (6)	3 (6)	
Noncomplicance with study drug	4 (2)	1 (2)	2 (4)	
Adverse event[a]	3 (1)	0	0	
Exacerbation of diarrhea	0	3 (5)	0	
Investigator's discretion	1 (1)	1 (2)	0	
Noncompliance with study visits	1 (1)	1 (2)	0	
Noncompliance with IVRS	1 (1)	0	0	
Repeated use of ADM or opiates	0	0	1 (2)	
Other[b]	5 (2)	2 (3)	3 (6)	

Source: Table 14.1.1 and 14.1.1pf, Section 14; corresponding Listing 16.2.1, Appendix 16.2.
Abbreviations: BID = twice daily; ADM = anti-diarrhea medication; IVRS = interactive voice response system; SD = standard deviation; AE = adverse event; PC = placebo controlled; PF = placebo free; SAP = statistical analysis plan.

a The number of subjects who discontinued due to AEs is different in this table and in Tables 14.3.1.4.1 and 14.3.1.4pf in Section 14.3. In the PC phase, 1 subject (0044-0006) experienced AEs that began in the PC phase and led to discontinuation from the study after completion of the PC phase. This subject was considered to have completed the PC phase in the disposition tables. In the PF phase, 4 subjects (0011-0053, 0035-0004, 0053-0005, and 0078-0009) were considered to have discontinued due to an AE on the AE page of the CRF, but the AE was not considered to be the primary reason for study discontinuation on the disposition page of the CRF.

b More detailed reasons for 'other' are provided for each subject in Listing 16.2.1 (Appendix 16.2).

Note: A total of 9 subjects from study (b) (4) were prospectively excluded from all analyses due to observations made by the FDA following an inspection conducted during (b) (4) The observations listed were detailed in the Form FDA 483 document (b) (4) and are also detailed in the SAP for the Interim Analysis Charter (see Attachment B of the SAP for the PC phase in Appendix 16.1.9.1.

Note: Four (4) subjects in the PF phase of Stage I had their crofelemer dose re-assigned by the investigator to a lower dose during the PF phase (Subjects 0014-0022, 0014-0024, 0049-0017, and 0058-0013; Listing 16.2.5.1). Per protocol, reassignment to the optimal crofelemer dose was possible if the investigator felt the response to the current dose was inadequate; investigators were blinded to the optimal dose and did not know if they were titrating subjects to a higher or lower dose, or the same dose.

Source: Table 7, Clinical Study Report for ADVENT

Two subjects did not take study medication and were excluded from the intent-to-treat population. One subject was randomized to crofelemer 125 mg bid and the other was randomized to crofelemer 500 mg bid.

Overall, most subjects were male (>84%) and had a mean age of about 45 years; see Table 3. The distribution of race, however, differed by stage. Within each treatment group in Stage I, 'White/Caucasian' was the most common race, ranging from 39% to 57% across the treatment

groups. The remaining subjects were almost evenly divided between 'Black/African American' and 'Other', with slightly more classified as 'Black/African American'. By contrast, in Stage II, 'Black/African American' was the most common race (crofelemer 125 mg bid – 42%; placebo – 44%).

The difference between stages in the distribution of race was due to a single site. Site #72 was the largest site and enrolled all 36 of its subjects during Stage II. The site was predominantly African-American (78%), male (92%), not Hispanic or Latino (92%) and had a mean age of 43 years. Among all other sites that enrolled subjects in Stage II, the proportion of subjects who were African-American (35%) or White/Caucasian (44%) more closely resembles the distribution seen in Stage I. As I discuss further in Section 4.1, there did not appear to be a crofelemer treatment effect among African-American subjects.

Table 3. Demographics for all subjects in the ITT population, and by stage; placebo-controlled treatment phase

Characteristic Category or statistic	Crofelemer 125 mg BID	Crofelemer 250 mg BID	Crofelemer 500 mg BID	Placebo BID
Combined (Stage I + Stage II)				
N	**136**	**54**	**46**	**138**
Age (years)				
Mean (SD)	45.0 (7.66)	43.8 (8.37)	45.8 (9.06)	44.8 (8.42)
Median (min, max)	45.0 (23, 61)	43.5 (24, 59)	46.0 (23, 68)	46.0 (21, 63)
Sex – n (%)				
Male	115 (84.6)	48 (88.9)	39 (84.8)	116 (84.1)
Female	21 (15.4)	6 (11.1)	7 (15.2)	22 (15.9)
Race – n (%)				
White/Caucasian	53 (39.0)	34 (63.0)	26 (56.5)	58 (42.0)
Black/African American	51 (37.5)	9 (16.7)	8 (17.4)	53 (38.4)
American Indian/Alaskan Native	1 (0.7)	1 (1.9)	0	0
Other[a]	31 (22.8)	10 (18.5)	12 (26.1)	27 (19.6)
Ethnicity – n (%)				
Hispanic or Latino	31 (22.8)	10 (18.5)	12 (26.1)	25 (18.1)
Not Hispanic or Latino	105 (77.2)	44 (81.5)	34 (73.9)	113 (81.9)

Characteristic Category or statistic	Crofelemer 125 mg BID	Crofelemer 250 mg BID	Crofelemer 500 mg BID	Placebo BID
Stage I				
N	**44**	**54**	**46**	**50**
Age (years)				
Mean (SD)	44.6 (8.18)	43.8 (8.37)	45.8 (9.06)	45.3 (7.94)
Median (min, max)	45.0 (23, 61)	43.5 (24, 59)	46.0 (23, 68)	46.0 (25, 63)
Sex – n (%)				
Male	38 (86.4)	48 (88.9)	39 (84.8)	41 (82.0)
Female	6 (13.6)	6 (11.1)	7 (15.2)	9 (18.0)
Race – n (%)				
White/Caucasian	18 (40.9)	34 (63.0)	26 (56.5)	25 (50.0)
Black/African American	12 (27.3)	9 (16.7)	8 (17.4)	14 (28.0)
American Indian/Alaskan Native	1 (2.3)	1 (1.9)	0	0
Other[a]	13 (29.5)	10 (18.5)	12 (26.1)	11 (22.0)
Ethnicity – n (%)				
Hispanic or Latino	13 (29.5)	10 (18.5)	12 (26.1)	11 (22.0)
Not Hispanic or Latino	31 (70.5)	44 (81.5)	34 (73.9)	39 (78.0)
Stage II				
N	**92**			**88**
Age (years)				
Mean (SD)	45.2 (7.44)			44.5 (8.71)
Median (min, max)	45.0 (24, 60)			46.0 (21, 62)
Sex – n (%)				
Male	77 (83.7)			75 (85.2)
Female	15 (16.3)			13 (16.3)
Race – n (%)				
White/Caucasian	35 (38.0)			33 (37.5)
Black/African American	39 (42.4)			39 (44.3)
Other[a]	18 (19.6)			16 (18.2)
Ethnicity – n (%)				
Hispanic or Latino	18 (19.6)			14 (15.9)
Not Hispanic or Latino	74 (80.4)			74 (84.1)

Source: Tables 14.1.4.1 and 14.1.4.3, Section 14.1; Listing 16.2.4.1, Appendix 16.2.
Abbreviations: BID = twice daily; SD = standard deviation; and CRF = case report form.
a In the subject CRFs, 'Hispanic' was listed as a selectable option for race. In the post-text and in-text demographic tables, subjects recorded as 'Hispanics' are summarized as an ethnicity and listed in the 'Other' category for race. With the exception of 2 subjects in the placebo group, all subjects captured in the 'Other' category had their race entered in the subject CRF as "Hispanic."

Source: Table 9, Clinical Study Report for ADVENT

Seventy sites (67 in the United States and 3 in Puerto Rico) randomized subjects. Among the subset of subjects who were randomized to either crofelemer 125 mg bid or placebo, the sites tended to be small with 17 sites randomizing only a single subject. The median number of subjects randomized to either crofelemer 125 mg bid or placebo per site was 3 subjects with an interquartile range of 1 subject to 4 subjects. The largest site (Site #72) enrolled 36 subjects (18 – crofelemer 125 mg bid, 18 – placebo), followed by three sites that clustered around 15 subjects (Sites 07, 14, and 25). The remaining sites enrolled 10 subjects or less.

Figure 7. A stem-and-leaf diagram depicting the number of subjects enrolled at each study site. The number of subjects is limited to those who were randomized to either crofelemer 125 mg bid or placebo. In the diagram, 'count' refers to the number of sites that enrolled the number of subjects defined by the stem and leaf; for example, one site (Count is 1) randomized a total 36 subjects ('3' is the stem and '6' is the leaf) to either crofelemer 125 mg bid or placebo.

Stem	Leaf	Count
3	6	1
3		
3		
3		
2		
2		
2		
2		
2		
1		
1	6	1
1	45	2
1		
1	0	1
0	8889	4
0	66777	5
0	4444444445	10
0	22222222222333333333333	24
0	11111111111111111	17

0|1 represents 1

Source: Statistical reviewer's analysis

As mentioned earlier, the largest site (Site #72) enrolled all of its subjects during Stage II and was predominantly African-American.

3.2.3 Statistical Methodologies

The study used an adaptive design to identify the dose that would be studied in Stage II. The plan called for Stage I to randomize 50 subjects to each of the four treatment groups, at which time enrollment was to be stopped. Once the subjects completed Stage I, an interim analysis was done to select the dose to be studied in Stage II. The decision regarding the timing of the interim analysis was not based on a power calculation, rather 'clinical judgment' as stated in the study protocol. Most of the study subjects were to be enrolled in Stage II. The interim analysis was not be used to adjust the sample size or to stop the study early for efficacy.

The primary efficacy analysis, which compared the proportion of responses in the placebo group to the proportion of responders in the crofelemer 125 mg group, used methodologies described by Posch et al (2005). The technique, which controls the family-wise type I error rate in the strong sense, uses closed testing principles. All pairwise comparisons with placebo, and their p-values, are needed for the analysis. Thus, within Stage I, the clinical response rate for each crofelemer treatment group (i.e., 125 mg, 250 mg, and 500 mg) was compared with the clinical response rate for the placebo treatment group. Within Stage II, the clinical response rate for crofelemer 125 mg was compared with the clinical response rate for placebo. Simulations were submitted when the protocol was under review to support the experiment-wise control of the Type I error rate of 2.5% (one-sided).

A one-sided test was used to assess whether the overall difference in clinical response rates between crofelemer 125 mg and placebo was less than zero or greater than zero, resulting in a one-sided p-value and a one-sided 97.5% confidence interval. The overall Type I error rate (one-sided) was 2.5%. The p-value and confidence interval were constructed by combining the results across the two stages. To calculate the overall p-value and confidence interval, the Applicant wrote a SAS macro into which are entered the number of subjects and number of responders for each treatment and stage; see Appendix 6-1. In order to combine the p-values from the two study stages, Posch et al requires p-values for tests of intersection hypotheses for Stage I. Simes test was used to generate these p-values.

Although the clinical study report indicates Wald statistics were used for all pairwise comparisons with placebo, my review concludes otherwise. First, Pearson chi-square tests – not Wald statistics – were used for the pairwise comparisons that the Applicant reported for the results summarized by study stage; for example, see Table 7 and Table 8 of my review. The test statistics were compared against a chi-square distribution to give the pairwise p-values shown in these tables. Further, my review of the SAS macro shows the one-sided confidence intervals presented in these tables are Yule confidence intervals. Note that 'Footnote a' to these tables is incorrect. The p-values and confidence intervals for the separate stages are not based on the Posch et al (2005) methodologies, which are directed at combining results across the stages and not at results within a stage. As I just described, the p-values are from Pearson chi-square tests and the confidence intervals are Yule intervals. Simes test was based on the results from the Pearson chi-square tests.

Data obtained during the last 7 days of the single-blind screening phase served as baseline for all statistical evaluations, including assessing change from baseline for the primary and secondary

efficacy variables. Baseline efficacy did not include the first 2 days of Screening, which was considered a washout period from anti-diarrheal medication (ADM) use.

Imputation was handled for clinical response as follows: A subject's data were evaluated for assessment of clinical response each week if at least 5 daily assessments per 7-day weekly period were available; that is, if 0, 1, or 2 days' data were missing, there was no imputation. If less than 5 days of data were available, then the subject was not classified as a responder for that week. Subjects who discontinued prematurely (i.e., before scheduled Visit 3) during the 4-week efficacy assessment period were classified as nonresponders.

Additionally, subjects who used an ADM or opiate pain medication, including any combination of ADM or opiate pain medication, for > 3 consecutive or non-consecutive days during the 4-week efficacy assessment period were classified as nonresponders.

3.2.4 Results and Conclusions

3.2.4.1 Interim analysis results that were used to select the dose that was studied in Stage II

The Interim Analysis Committee selected the 125 mg dose because it had the largest treatment effect of 8%, compared with 1% for 250 mg and 5% for 500 mg; see Table 4. The committee did not believe these magnitudes were clinically meaningful but, based on the prespecified decision rule and the lack of severe adverse events for the 125 mg dose, made an unanimous recommendation to proceed with the 125 mg dose. The committee expressed puzzlement that the 125 mg dose had the largest number of AEs (36%) and that most of these AEs were GI disorders (18%).

Table 4. Stage I, Interim Analysis: Clinical Response, based on IVRS data only and the data from the 3-day run-in

Clinical Response – Stage I	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo BID n (%)
N	45	54	47	50
Experienced Clinical Response	9 (20)	7 (13)	8 (17)	6 (12)
Did Not Experience Clinical Response	36 (80)	47 (87)	39 (83)	44 (88)

Source: ADVENT Dose Selection Report.
Abbreviations: BID = twice daily.
Note: Clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the placebo-controlled treatment phase.

Source: Table 19, Clinical Study Report, ADVENT

The committee attempted to understand why the results in the ADVENT trial were poor compared to an earlier trial:

> The committee tried to understand why the results in the current trial were so poor as compared to its predecessor trial conducted by Shaman Pharmaceuticals in which the primary endpoint was based on stool weight. The committee expressed the opinion that the choice of primary endpoint, no more than two watery bowel movements in at least two of the four weeks of the placebo controlled phase, was an extremely stringent criterion for demonstrating efficacy. In addition, the committee was concerned that the inclusion criteria were too broad and that a better performance might have been observed with a more restrictive eligibility rule based on the etiology of the symptom, and either limiting inclusion to those patients with diarrhea plausibly attributable to HIV infection alone (quite difficult to define) or have at least documented those starting and maintaining contributants etiologies, such as bacterial overgrowth and/or fat malabsorption. This would focus the endpoint on indexing reductions related more to HIV enteropathy. This compound would only have an effect on secretory diarrhea. *For further elaboration on this point and other possible causes of failure to show efficacy, please refer to the additional note submitted by* (b) (4) *after the meeting.*

Source: Minutes of the Interim Analysis Committee meeting, 8/3/2009

However, the response rates reviewed by the Interim Analysis Committee were not correct and, in fact, the final estimates of the treatment effects were larger than those reviewed by the committee; see Table 5 (below) and Section 11.4.1.3 of the Clinical Study Report. The reasons for these differences are explained in the following paragraphs.

First, the interim analysis was not done correctly, because the analysis included information from the three-day run-in period following randomization. The protocol specified that all efficacy analyses would exclude results from the run-in period and would be based solely on data from the four-week efficacy assessment period. As a result, two placebo subjects and two crofelemer *250 mg* subjects were considered responders in the interim analysis but not the final analysis[4]. Additionally, one crofelemer *500 mg* subject was a responder in the final analysis but not in the interim analysis.

Second, the interim analysis relied only on the eDiary data, which were captured by the IVRS, in order to determine whether subjects had used ADMs or opioid medications for more than three days and, thus, would be classified as non-responders. The final analysis included an additional source of information on the use of the medications – the eCRF. When prohibited medications identified by the eCRF were taken into account, three placebo-treated subjects who were responders in the interim analysis were counted as non-responders in the final analysis.

[4] In this review and in the NDA, "final analysis" refers to the set of analyses that were done after the final data lock, and should not be confused with the final analysis done when using interim analysis methods that are intended to assess whether a study can be stopped early if the study satisfies early stopping rules. The final data set included changes to the outcomes for some subjects who were classified at the interim analysis as clinical responders or non-responders. These changes occurred when results from the three-day run-in period were excluded, and when ADM and opiate pain medication use from the eCRF were considered in addition to the eDiary data only.

Table 5. Stage I, Final Analysis: Clinical Response, excludes 3-day run-in and includes CRF ADM/Opiate data

Parameter/Statistic[a, b]	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo BID n (%)
Responder – n/N (%)	9/44 (20.5%)	5/54 (9.3%)	9/46 (19.6%)	1/50 (2.0%)
Treatment Difference	18.5%	7.3%	17.6%	---
1-sided 97.5% CI for Diff.	[6.0%, ∞)	[-1.7%, ∞)	[5.3%, ∞)	---
1-sided p-value (vs. placebo)	0.0019	0.0563	0.0024	---

Source: Tables 14.2.1.1, Section 14.2; Listing 16.2.6.2, Appendix 16.2
Abbreviations: BID = twice daily; CI = confidence interval; ITT = intent-to-treat.
Note: Clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the placebo-controlled treatment phase.
a P-values and CIs were calculated based on the methods of Posch and Bauer (2005).
b If less than 5 days of data were available in a week, the subject was classified as a non-responder for that week. Subjects who discontinued prematurely during the 4-week period were classified as non-responders. Subjects who used an ADM or opiate pain medication for > 3 days during the efficacy assessment period were also non-responders.

Statistical Reviewer's note: The p-values and confidence intervals are not adjusted for multiple comparisons and should not be used for making conclusions regarding pairwise comparisons between each treatment group and placebo. Moreover, 'Footnote b' is incorrect – the p-values and confidence intervals presented for this single stage are not based on the methods of Posch and Bauer (2005) that are intended for p-values and confidence intervals for data combined across two stages of an adaptive design; the p-values are based on asymptotic Pearson chi-square tests and the confidence intervals are Yule confidence intervals.

Source: Table 17, Clinical Study Report, ADVENT

3.2.4.2 Applicant's efficacy results

The application reports that among subjects randomized to crofelemer 125 mg BID, the proportion who had a clinical response was significantly greater than among subjects randomized to placebo (Table 6). The treatment difference was 9.6% (17.6% for crofelemer vs. 8.0% for placebo) with a one-sided 97.5% confidence interval of [1.2%, ∞].

Table 6. Clinical Response Results for 125 mg BID and Placebo BID

Parameter/Statistic[a]	Crofelemer 125 mg BID n (%)	Placebo BID n (%)
Combined Analysis (Stage I + Stage II)[b]		
Responder – n/N (%)	24/136 (17.6%)	11/138 (8.0%)
Treatment Difference	9.6%	--
1-sided 97.5% CI for Diff.	[1.2%, ∞)	--
1-sided p-value (vs. placebo)	0.0096	--

Source: Table 14.2.1.1, Section 14.2; Listing 16.2.6.2, Appendix 16.2
Abbreviations: BID = twice daily; CI = confidence interval; ITT = intent-to-treat.
Note: Clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the PC phase.
a P-values and CIs were calculated based on the methods of Posch and Bauer (2005).
b If less than 5 days of data were available in a week, the subject was classified as a non-responder for that week. Subjects who discontinued prematurely during the 4-week efficacy assessment period were classified as non-responders. Subjects who used an ADM or opiate pain medication for > 3 days during the efficacy assessment period were also non-responders.

Source: Table 16, Clinical Study Report for ADVENT

The clinical study report notes the treatment difference and the statistical significance of the difference, however, were not consistent across the two study stages; see Table 7 and Table 8. The Stage I treatment difference was larger (18.5%) than in Stage II (4.9%), and was also statistically significant (one-sided p-value=0.002 in Stage I vs. one-sided p-value=0.169 in Stage II) despite a larger sample size in Stage II. Inspection of the response rates suggests the inconsistent results could be due to an increase in the placebo response rate from Stage I (2.0%) to Stage II (11.4%), and a slight decrease in the crofelemer response rate from Stage I (20.5%) to Stage II (16.3%).

Table 7. Clinical Response Rates for Stage I

Parameter/Statistic[a, b]	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo BID n (%)
Responder – n/N (%)	9/44 (20.5%)	5/54 (9.3%)	9/46 (19.6%)	1/50 (2.0%)
Treatment Difference	18.5%	7.3%	17.6%	---
1-sided 97.5% CI for Diff.	[6.0%, ∞)	[-1.7%, ∞)	[5.3%, ∞)	---
1-sided p-value (vs. placebo)	0.0019	0.0563	0.0024	---

Source: Tables 14.2.1.1, Section 14.2; Listing 16.2.6.2, Appendix 16.2
Abbreviations: BID = twice daily; CI = confidence interval; ITT = intent-to-treat.
Note: Clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the placebo-controlled treatment phase.
a P-values and CIs were calculated based on the methods of Posch and Bauer (2005).
b If less than 5 days of data were available in a week, the subject was classified as a non-responder for that week. Subjects who discontinued prematurely during the 4-week period were classified as non-responders. Subjects who used an ADM or opiate pain medication for > 3 days during the efficacy assessment period were also non-responders.

Statistical Reviewer's note: The p-values and confidence intervals are not adjusted for multiple comparisons and should not be used for making conclusions regarding pairwise comparisons between each treatment group and placebo. Moreover, 'Footnote b' is incorrect – the p-values and confidence intervals are not based on the methods of Posch and Bauer (2005) that are intended for p-values and confidence intervals for data combined across two stages of an adaptive design; the p-values are based on asymptotic Pearson chi-square tests and the confidence intervals are Yule confidence intervals.

Source: Table 17, Clinical Study Report for ADVENT

Table 8. Clinical response rates for Stage II

Parameter/Statistic[a, b]	Crofelemer 125 mg BID n (%)	Placebo BID n (%)
Responder – n/N (%)	15/92 (16.3%)	10/88 (11.4%)
Treatment Difference	4.9%	--
1-sided 97.5% CI for Diff.	[-5.2%, ∞)	--
1-sided p-value (vs. placebo)	0.1690	--

Source: Tables 14.2.1.1 and 14.2.1.2, Section 14.2; Listing 16.2.6.2, Appendix 16.2
Abbreviations: BID = twice daily; CI = confidence interval; ITT = intent-to-treat.
a P-values and CIs were calculated based on the methods of Posch and Bauer (2005).
b If less than 5 days of data were available in a week, the subject was classified as a non-responder for that week. Subjects who discontinued prematurely during the 4-week period were classified as non-responders. Subjects who used an ADM or opiate pain medication for > 3 days during the efficacy assessment period were also non-responders.

Statistical Reviewer's note: The p-values and confidence intervals are not adjusted for multiple comparisons and should not be used for making conclusions regarding pairwise comparisons between each treatment group and placebo. Moreover, 'Footnote b' is incorrect – the p-values and confidence intervals are not based on the methods of Posch and Bauer (2005) that are intended for p-values and confidence intervals for data combined across two stages of an adaptive design; the p-values are based on asymptotic Pearson chi-square tests and the confidence intervals are Yule confidence intervals.

Source: Table 20, Clinical Study Report for ADVENT

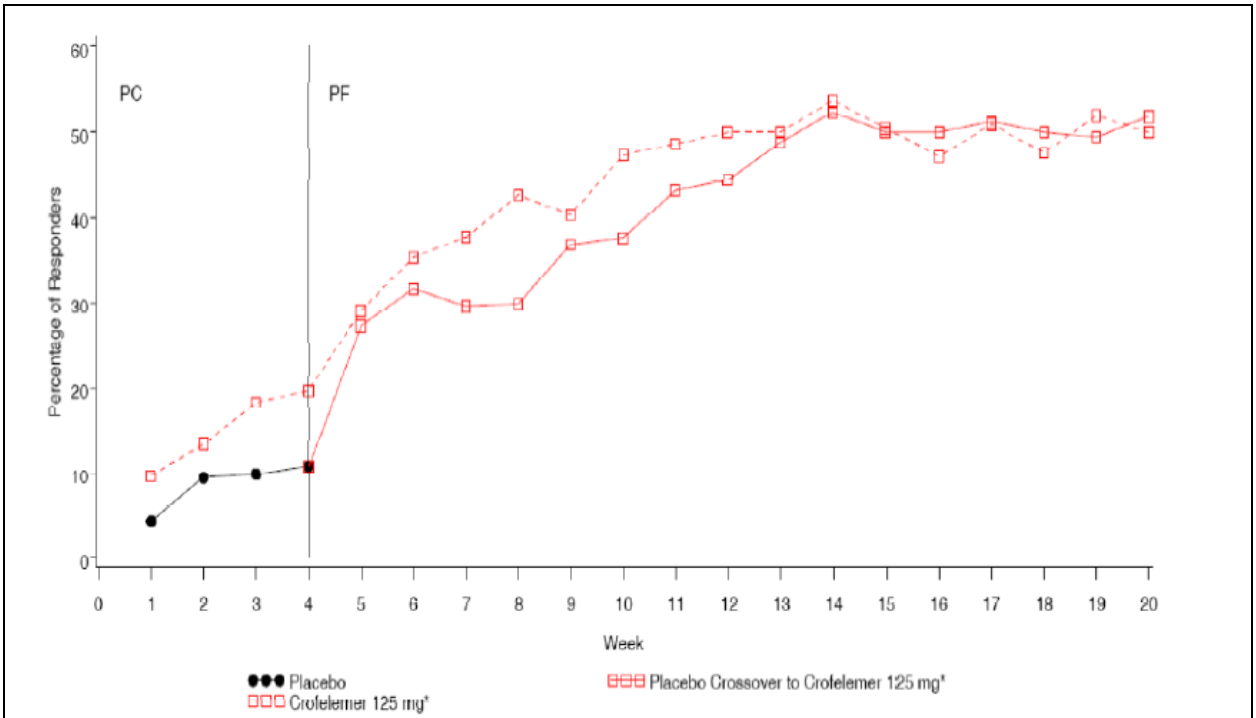
Based on the results of exploratory analyses conducted by the Applicant in an attempt to identify possible reasons for these differences across study stage, the Applicant concluded (see Section 11.4.1.4.2, page 97 of clinical study report):

> "In summary, the between-stage imbalance in baseline watery bowel movements explains why the crofelemer treatment difference was statistically significant in Stage I, but not in Stage II. The statistically significant result in favor of crofelemer in the combined analysis (primary endpoint) was likely due to crofelemer's pronounced treatment effect across study stages in subjects with more clinically significant diarrhea, as described in Sections 11.4.1.5 and 11.4.1.6."

To demonstrate durability of the treatment effect of crofelemer 125 mg, the Applicant generated Figure 8, (b) (4) The first part of the figure (Week 1 – Week 4) shows the weekly response rates during the placebo-controlled phase; the second part (Week 5 – Week 20) shows the weekly response rates during the placebo-free phase for the subjects who continued into the placebo-free phase. The top line shows the weekly response rates for subjects who were randomized to crofelemer 125 mg. The bottom line shows the weekly response rates for *all* placebo-treated subjects during Week 1 – Week 4, and then the weekly response rates for only the placebo-treated subjects who crossed over to crofelemer 125 mg and continued into the placebo-free phase. Note that the response rates are limited to only those subjects who remained in the study. Those who discontinued from the study are eliminated from the denominator used to calculate the response rates.

The Applicant concludes (page 108 of the clinical study report) "over 20 weeks of treatment there was not evidence of a decline [in] the crofelemer response rate during long-term use, indicating sustained efficacy."

Figure 8. Reproduction of Applicant's figure of percentage of subjects with clinical response by week. This figure appears in the (b) (4) clinical study report and depicts weekly clinical response rates among subjects who remain in the study; dropouts are excluded from the calculations of response rates. The PC phase contains all subjects randomized to placebo or crofelemer 125 mg. The PF phase depicts PC phase subjects who chose to continue in the PF phase and excludes placebo-treated subjects who crossed over to crofelemer 250 mg or crofelemer 500 mg.



Source: Figure 14.2.2.1, Section 14.2; Listing 16.2.6.1, Appendix 16.2
Abbreviations: PC = placebo-controlled treatment phase; and PF = placebo-free extension phase.

Source: Figure 9 of clinical study report, page 108.

3.2.4.3 Statistical reviewer's analyses and assessments

3.2.4.3.1 An exploration of differences between Stage I and Stage II

Whenever interim analyses are conducted, including those for two-stage adaptive designs, it is important to investigate whether operational bias is introduced into a study in a way that influences the results of the study. In the case of ADVENT, there are notable differences between the two stages:

- Smaller treatment difference in Stage II, and difference is statistically non-significant
- Higher completion rates in Stage II
- Largest study site enrolled all its subjects in Stage II

The treatment effect for Stage II was smaller than the treatment effect for Stage I, despite a larger sample size in Stage II. According to the Applicant, possible reasons for this inconsistent treatment effect include a higher placebo response rate in Stage II (11.4%) compared with Stage I (2.0%). They noted an imbalance across stages in baseline watery bowel movements in the placebo treatment groups; see Table 9. An exploratory analysis suggested the crofelemer treatment effect was more pronounced with subjects who began the study with >2 daily water bowel movements; see Table 10. The Applicant concludes that because "subjects … with more severe baseline watery stools were unlikely to experience clinical benefit in the study without crofelemer treatment," then "a pronounced crofelemer treatment effect was observed in Stage I, as placebo subjects in Stage I had a significantly greater number of baseline watery stools than in Stage II"; see page 97 of clinical study report.

Table 9. Applicant's analysis showing unbalanced distribution of daily watery bowel movements at baseline for Stage I and Stage II.

Baseline Daily Watery Bowel Movements	Crofelemer 125 mg BID		Placebo BID		Overall	
	Stage I (N=44)	Stage II (N=92)	Stage I (N=50)	Stage II (N=88)	Stage I (N=94)	Stage II (N=180)
Mean (SD)	2.86 (1.62)	2.63 (1.67)	3.52 (2.68)	2.78 (1.61)	3.21 (2.26)	2.70 (1.64)
p-value[a]	0.4575		0.0443		0.0348	

Source: Table 14.1.5.4, Section 14.1
Abbreviations: BID = twice daily; and ITT = intent-to-treat.
a P-values for testing the differences between study stages were performed using a chi-square test for character variables and a t-test for continuing variables.

Source: Table 21 of the clinical study report, page 97

Table 10. Applicant's analysis showing clinical responders by number of daily watery stools (≤2 or >2) at baseline.

Parameter/Statistic[a, b]	Crofelemer 125 mg BID (N=136)	Placebo BID (N=138)	p-value
Clinical Responders – n/N (%)			
> 2 Baseline Daily Watery Bowel Movements	9/75 (12.0)	2/83 (2.4)	0.0260
≤ 2 Baseline Daily Watery Bowel Movements	15/61 (24.6)	9/55 (16.4)	0.3597

Source: Table 14.2.1.7, Section 14.2; Listing 16.2.6.1, Appendix 16.2.
Abbreviations: BID = twice daily; and ITT = intent-to-treat.
a P-values were obtained using Fisher's exact test.

Source: Table 22 of the clinical study report, page 97

I do not agree with the Applicant's conclusions. As discussed below, the data suggest there were two subjects with outlying values who may account for the differences at baseline. Also, the point estimate of the treatment effect among those with >2 baseline watery bowel movements (9.6) is about the same as the point estimate for those with ≤2 baseline watery bowel movements (8.2). That one comparison is statistically significant and the other is not does not mean the crofelemer effect is more pronounced in one of the subgroups. Because the size of the treatment

effect is consistent among the two subgroups, the data suggest that overall response is dependent on the number of baseline daily watery bowel movements, regardless of treatment group – overall response is higher among those with ≤2 baseline watery bowel movements (21%) than among those with >2 baseline watery bowel movements (7%).

An increase in the standard deviation in the Stage I – placebo subjects (2.68) compared with the consistent standard deviation among all other treatment groups (range of standard deviation: 1.61 to 1.67) suggests the possibility of outlying observations in the Stage I – placebo subjects. Indeed, descriptive statistics show that only the maximum value differs across the four groups. The maximum value of 15.3 occurs in Stage I – Placebo (subject ID = HV101-0053-0005). Inspection of the baseline watery bowel movement values show the next highest value among the four groups is 11.14, which is also in Stage I – placebo (subject ID = HV101-0063-0015), followed by 9.7 in Stage II – Placebo.

Table 11. Descriptive statistics for Baseline Daily Watery Bowel Movements by Treatment Group and Stage

Baseline Daily Watery Bowel Movements	Crofelemer 125 mg BID		Placebo BID	
	Stage I	Stage II	Stage I	Stage II
Maximum	7.7	7.9	15.3	9.7
75th percentile	4.0	3.3	4.2	3.4
Median	2.6	2.2	2.7	2.4
25th percentile	1.6	1.4	1.7	1.6
Minimum	0.7	0.0	1.1	0.9

Overall, these findings do not suggest the introduction of operational bias between Stage I and Stage II that could have influenced the study outcomes to favor crofelemer. In fact, the results for Stage II have a smaller treatment effect than what was observed for Stage I.

3.2.4.3.2 Durability of crofelemer's effect

Because crofelemer's effect is modest (i.e., crofelemer 125 mg – 18% clinical response rate vs. placebo – 10% clinical response rate), the durability of crofelemer's effect is an important review issue. Durability is best evaluated in the context of a blinded, randomized study.

However, for ADVENT, any information pertaining to the durability of crofelemer's effect must come from the open-label, placebo-free phase of the study. The weaknesses of using the placebo-free phase to evaluate durability include:

- Results may be biased because data come from only those subjects who chose to participate in the placebo-free phase; randomization is not preserved.
- Results may be biased because the placebo-free phase is not blinded. The knowledge that subjects are receiving active treatment could influence outcomes.

Because the open-label, placebo-free phase of the study does not allow a comparison with a randomized control arm, one way to assess the durability of crofelemer's effect is to limit the analysis to subjects who were classified as clinical responders at the end of the placebo-controlled phase and who agreed to continue into the placebo-free phase. The next step is to determine the duration of their clinical response during the PF phase.

At the end of the PC phase, there were a total of 46 clinical responders who continued into the PF phase (Table 12). These participants include all placebo-treated subjects (n=11) who were responders at the end of the PC phase and almost all crofelemer 125 mg treated subjects (22 of 24) who were responders at the end of the PC phase.

Of the 22 crofelemer 125 mg responders who entered the PF phase, 14 were responders through every month of the PF phase; however, five were non-responders by Month 3. Based on these relatively small numbers of subjects, the results suggest a reasonable number of the crofelemer 125 mg responders maintained their response. However, this needs to be balanced by the finding that five of the subjects had lost their response to treatment by Month 3 of the PF phase.

Table 12. Durability of effect among subjects who were clinical responders at the end of the placebo-controlled (PC) phase

Yes = responder; No = non-responder; - = unknown					**Placebo N=11**	**125 mg N=22**	**250 mg N=5**	**500 mg N=8**
Month 1	Month 2	Month 3	Month 4	Month 5	Number of responders			
Yes	Yes	Yes	Yes	Yes	7	14	2	5
Yes	Yes	Yes	Yes	-	-	-	1	-
Yes	Yes	Yes	No	No	-	1	-	-
Yes	Yes	Yes	-	-	1	-	1	-
Yes	Yes	Yes	No	Yes	-	1	-	-
Yes	Yes	No	Yes	Yes	1	1	-	1
Yes	Yes	No	Yes	No				1
Yes	No	Yes	Yes	Yes	1	-	-	-
Yes	No	-	-	-	1	2	-	-
No	No	Yes	No	No	-	-	1	1
No	No	-	-	-	-	1	-	-
No	-	-	-	-	-	2	-	-

Source: Statistical Reviewer's analysis

(b) (4)

In order to understand the weaknesses of the figure, I first describe how it was generated. The figure is divided into two parts: the placebo-controlled (PC) phase and the placebo-free (PF) phase. The PC phase of the figure contains all subjects randomized to crofelemer 125 mg and all subjects randomized to placebo who crossed over to any crofelemer dose. The PF phase of the figure is limited to those subjects who chose to continue their participation in the study. In addition, the PF phase of the figure excludes placebo-treated subjects who crossed over to

crofelemer 250 mg or crofelemer 500 mg. Finally, the weekly response rates are limited only to those subjects who remained in the study; data from dropouts are excluded.

There are four major weaknesses to the information depicted in the figure. First, the subjects depicted in the PC phase are a subset of the subjects depicted in the PC phase. Thus, a visual comparison of the subjects in the PF phase with the subjects in the PC phase is actually a comparison of different sets of subjects. This is particularly pronounced among the placebo-treated subjects, because the PC phase shows all subjects randomized to placebo (n=138) while the PF phase shows only the placebo subjects (n=99) who crossed over to crofelemer 125 mg in the PF phase. Thus, a visual comparison of the placebo subjects who crossed over to crofelemer 125 mg (n=99) with the placebo-treated subjects in the PC phase (n=138) can not be used to support a conclusion that subjects randomized to placebo had an increase in their response rates when crossed over to crofelemer 125 mg. Similarly, the crofelemer-treated subjects who entered the PF phase (n=121) are a subset of those who were randomized to crofelemer 125 mg (n=136), and the comparison of those who enrolled in the PF phase with those in the PC phase is also problematic.

Second, because all subjects knew they were receiving active treatment when they entered the PF extension phase, it is quite possible that this knowledge alone accounts for the increase in response rates observed during the first week of the placebo-free extension phase, both for placebo-treated subjects and for crofelemer 125 mg subjects. During the first week of the PF phase, among those who were clinical non-responders at the end of the PC phase, the clinical response rates were 19% (17/88) for placebo subjects who crossed over to crofelemer 125 mg and 13% (13/99) for subjects who continued on crofelemer 125 mg[5]. The 13% response rate among the crofelemer 125 mg non-responders suggests the possibility that most of the 19% clinical response rate observed for placebo subjects who switched to crofelemer 125 mg may simply be due to the open-label nature of the study.

Third, the graph contains a mixture of subjects who were clinical responders at the end of the PC phase and subjects who were clinical non-responders at the end of the PC phase. Thus, a conclusion of treatment durability is also based on the results of subjects who were non-responders at the end of the PC phase.

Finally, the supporting data and the response to an information request[6] show the calculation of weekly response rates is limited to those subjects who remained in the study. Subjects who dropped out of the study are not subsequently considered in the calculation of weekly response rates. As a general principle, in most clinical trials, subjects who are benefitting from treatment are more like to participate in open-label study extensions. As a result, the response rates limited to responders are usually overestimates of the true response rates. This appears to be the case with this study as shown in the following analyses.

[5] Response to FDA Request for Information, response submitted 7/13/2012, Sequence 018 summarizes the number and percentages of first-time clinical weekly responders for both the PC phase and the PF phase; see Appendix 6-2. I recalculated the rates for those who were clinical non-responders.

I requested analyses[6] from the Applicant that:

- Counts dropouts as non-responders
- Limits the placebo subjects in the PC phase to only those who crossed over to crofelemer 125 mg in the placebo-free phase.
- Limits the crofelemer 125 mg subjects in the PC phase to only those subjects who participated in the placebo-free phase.

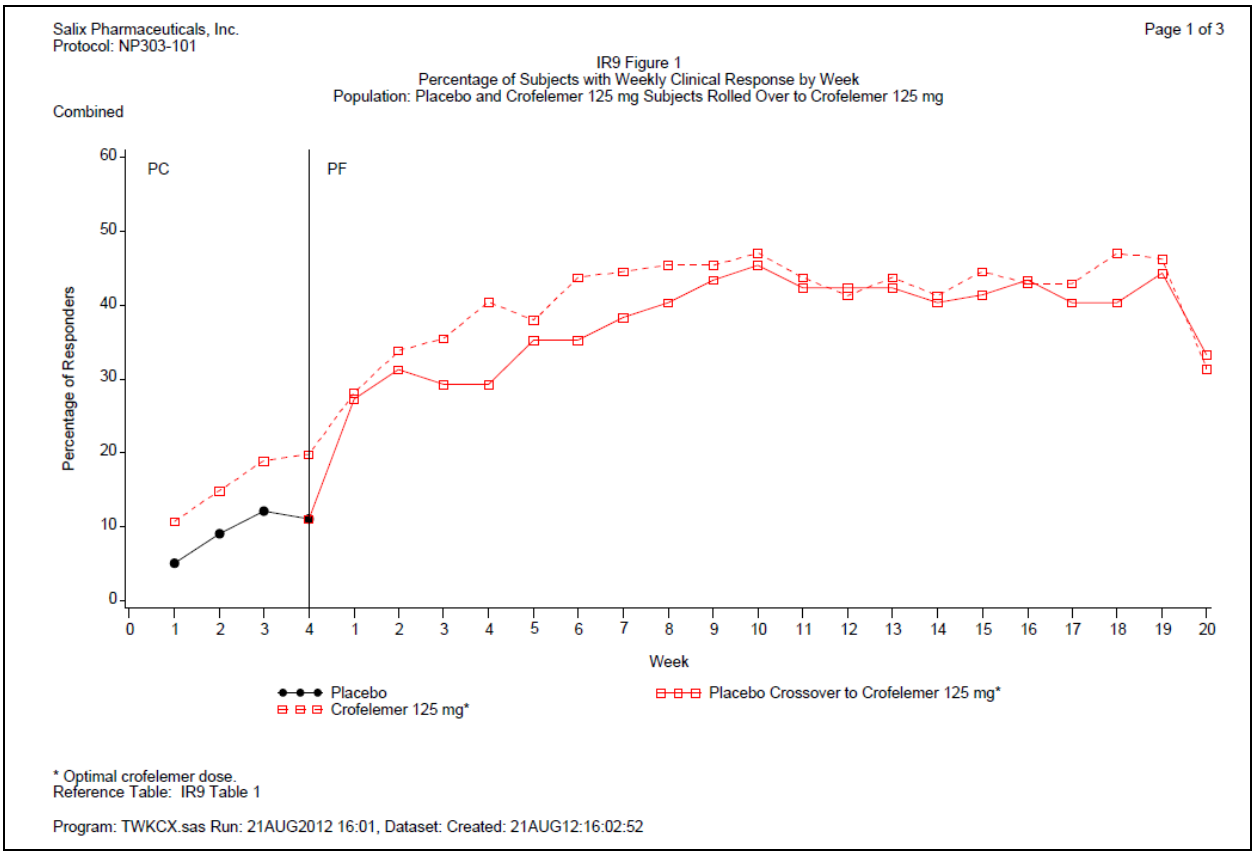
I also requested new figures that include these stipulations.

As shown in Figure 9, these analyses resulted in a reduction of the clinical response rates from those displayed in Figure 8. When interpreting these figures, it is important to keep in mind that the results are limited to subjects who chose to participate in the PF phase and are likely overestimates of the true response rates.

The results by stage show the patterns seen in Stage I (Figure 10) are more variable than those seen in Stage II (Figure 11). Stage II (Figure 9) mirrors what is seen for all subjects combined, namely an increase in clinical response rates among subjects randomized to placebo.

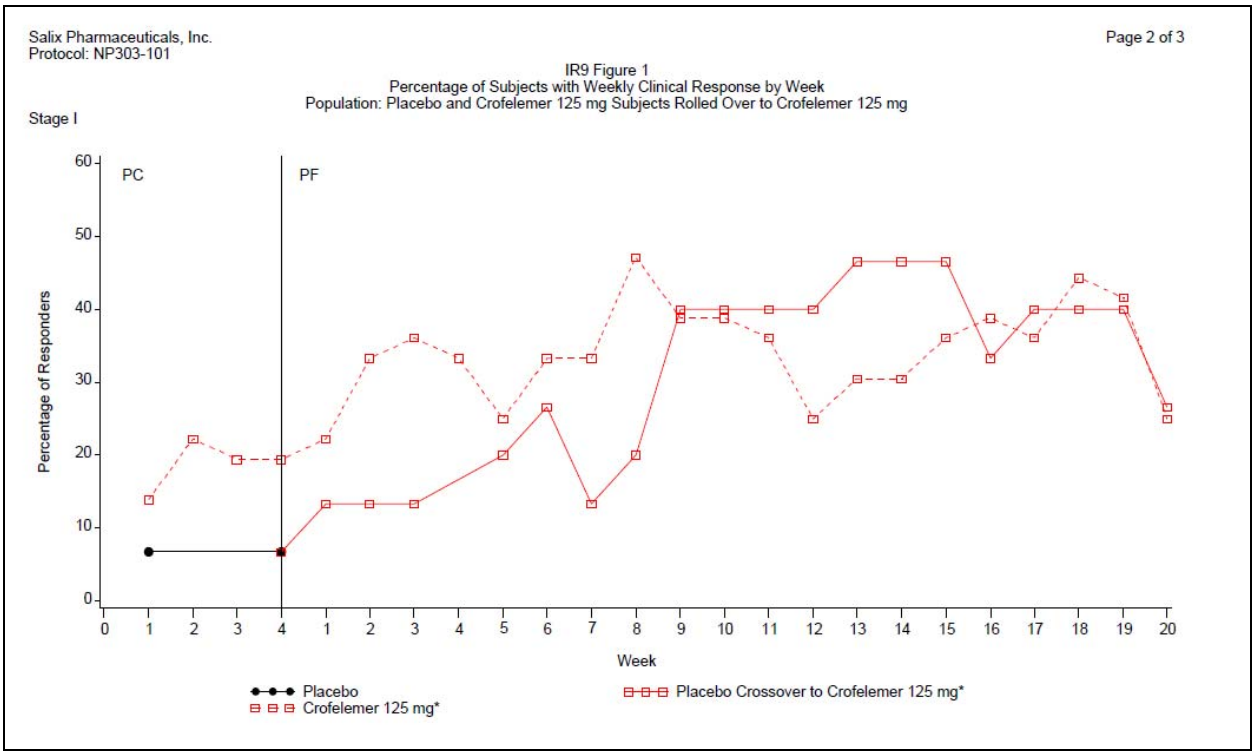
[6] Response to FDA Request for Information, response submitted 7/13/2012, Sequence 018 and Response to FDA Request for Information, response submitted 8/22/2012, Sequence 024.

Figure 9. Overall: Weekly clinical response rates restricted to placebo-subjects in the PC phase who crossed over to crofelemer 125 mg (n=99) and crofelemer 125 mg subjects who continued into the PF phase (n=121); PF dropouts are counted as non-responders.



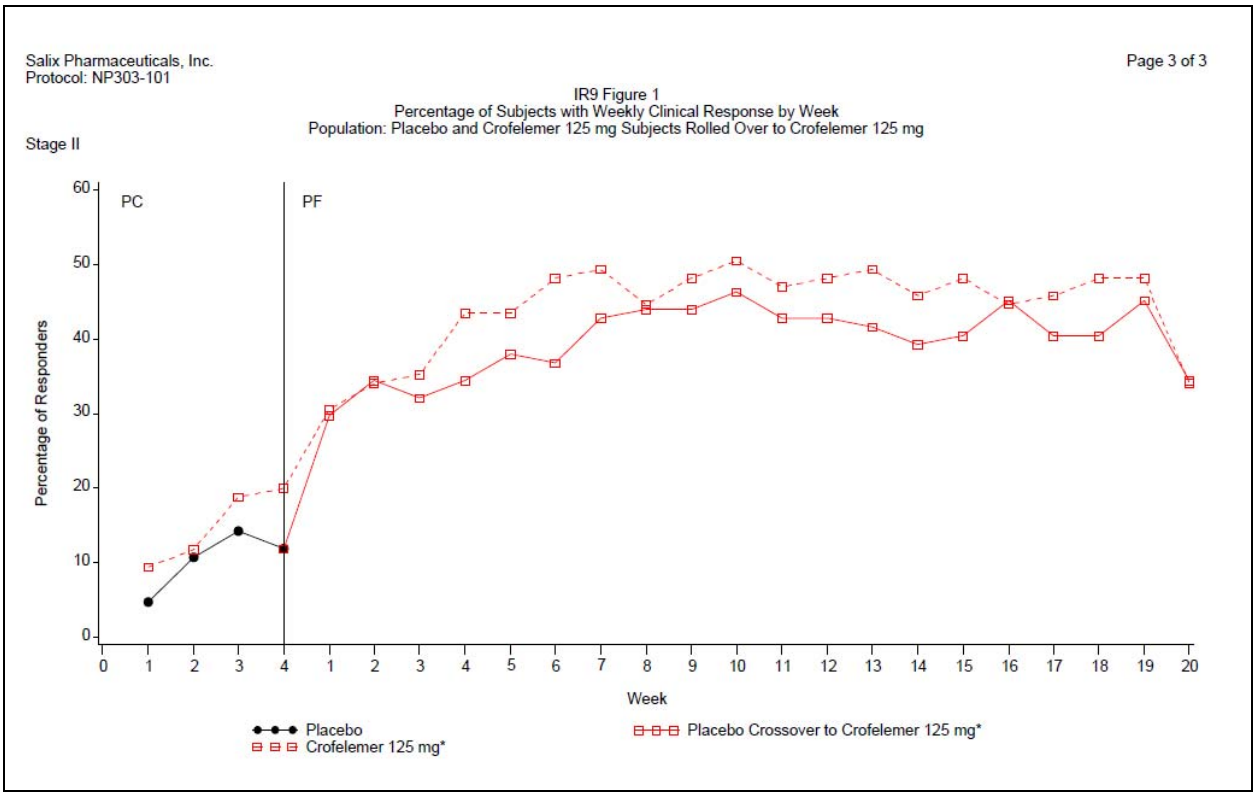
Source: Response to FDA Request for Information, response submitted 8/22/2012, Sequence 024

Figure 10. Stage I: Weekly clinical response rates restricted to placebo-subjects in the PC phase who crossed over to crofelemer 125 mg and c crofelemer 125 mg subjects who continued into the PF phase; PF dropouts are counted as non-responders.



Source: *Response to FDA Request for Information, response submitted 8/22/2012, Sequence 024*

Figure 11. Stage II: Weekly clinical response rates restricted to placebo-subjects in the PC phase who crossed over to crofelemer 125 mg and crofelemer 125 mg subjects who continued in the PF phase; PF dropouts are counted as non-responders.



Source: *Response to FDA Request for Information, response submitted 8/22/2012, Sequence 024*

3.2.4.3.3 Recalculation of p-value and Type I error rate for the comparison of the crofelemer 125 mg and placebo treatment groups

Although two reasons led me to question the overall p-value of 0.0096 (one-sided), this p-value appears to be appropriate for the hypothesis test of no difference between crofelemer 125 mg and placebo in the clinical response rates. The reasons for questioning the overall p-value are as follows. First, because of the relatively small clinical response rates that were observed for the treatment groups (range: 2% to 20%), exact methods appeared to be more appropriate for calculating the p-values associated with the pairwise comparisons of treatment with placebo than the asymptotic methods used to calculate the pairwise p-values needed for the Posch et al methodology. Therefore, it was possible that the overall p-value of 0.0096 (one-sided) was incorrect.

Second, the simulations submitted to the IND when the protocol was being reviewed showed Type I error rates of about 2.5% when the response rates were assumed to range from 30% to 55%, response rates that are much greater than what was observed for ADVENT and that are consistent with the assumptions underlying the use of asymptotic distributions. As a result, I was

concerned that the overall Type I error rate might be greater than 2.5%, leading to an erroneous conclusion of statistical significance for the difference between crofelemer 125 mg and placebo.

Because of the small clinical response rates that were observed for the treatment groups, I investigated the effect on the overall conclusions if exact methods were used to calculate the pairwise p-values needed for the Posch et al methodology. In addition, I requested new simulations showing the overall Type I error rate when the assumed response rates are consistent with the rates that were observed in ADVENT. Interestingly, although the size of the p-values for the pairwise comparisons generally doubled in size (Table 13), the overall Type I error rate of 2.5% was maintained when the asymptotic distributions were used (Table 14).

Table 13. Pearson chi-square p-values (one-sided) for pairwise treatment comparisons, using exact and asymptotic distributions.

Comparison	Stage I		Stage II	
	Asymptotic	Exact	Asymptotic	Exact
Crofelemer 125 mg vs. Placebo	.0019	.0042	.1690	.2293
Crofelemer 250 mg vs. Placebo	.0563	.1212	n/a	n/a
Crofelemer 500 mg vs. Placebo	.0024	.0052	n/a	n/a

Source: Asymptotic p-values – Tables 17 and 20 from the ADVENT clinical study report; exact p-values – Statistical Reviewer's analysis using StatXact

The simulations submitted to the IND when the protocol was being reviewed showed Type I error rates of about 2.5% when the response rates were assumed to range from 30% to 55%, response rates that are much greater than those observed for ADVENT. I requested the Applicant to redo the simulations by using exact tests for the pairwise comparisons and by assuming response rates and sample sizes on the order observed for ADVENT. The Type I error rates when the asymptotic tests are used are approximately 2.5% whereas the Type I error rates associated with the exact tests are much more conservative (Table 14). Therefore, the use of the asymptotic methods that resulted in the overall p-value of 0.0096 appear appropriate for ADVENT.

Table 14. Type I error rates for exact and asymptotic methods

Table 1: Type-1 Error Rates for Exact and Asymptotic Methods (100,000 Simulated Trials)

Simulation Parameters				Type-1 Error Rate	
Placebo (π_0)	125 mg (π_1)	250 mg (π_2)	500 mg (π_3)	Exact	Asymptotic
0.02	0.02	0.02	0.02	17	2133
0.05	0.05	0.05	0.05	355	2262
0.1	0.1	0.1	0.1	653	2367
0.2	0.2	0.2	0.2	932	2216
0.3	0.3	0.3	0.3	1044	2156
0.4	0.4	0.4	0.4	1110	2258
0.5	0.5	0.5	0.5	1080	2248

Source: Response to FDA Request for Information, response submitted 7/13/2012, Sequence 018

3.2.4.3.4 Definition of primary endpoint and its relationship to study entry criteria

The definition of the primary endpoint overlaps with the study's inclusion criteria. Potentially, subjects may have qualified as clinical responders at study entry. Therefore, it is important to explore how this overlap affected the interpretation of the study results.

In order to enter the study, a subject had to report at least 1 or more watery bowel movements per day on at least 5 of the last 7 days of the single-blind placebo screening phase. In the efficacy analyses, a subject who reported two or less watery bowel movements per week during at least two of the four weeks of the efficacy assessment period of the placebo-controlled treatment phase was classified a clinical responder, unless they used ADMs or opiates for >3 days.

To investigate the possibility of a relationship between clinical response status at study entry and crofelemer's treatment effect, I calculated the response rates for subgroups defined by baseline number of watery bowel movements (≤ 2, > 2) that were consistent with the definition of a clinical responder. Among subjects with ≤ 2 watery bowel movements at baseline, overall, around 21% were responders at the end of the study (24/115) compared with 7% among subjects with >2 watery bowel movements at baseline (11/157). Within each subgroup the treatment effect was about the same; 10% vs. 8%; Table 10.

A slightly different picture emerges when these rates are compared across study stage. Among subjects with ≤ 2 watery bowel movements at baseline, the treatment effect was 12% in Stage I compared with no effect in Stage II; Table 15. Among subjects with >2 watery bowel movements at baseline, a treatment effect was observed in both stages (Stage I: 16%; Stage II: 6%); Table 16.

Table 15. Clinical response rates by study stage: subjects with baseline watery bowel movements ≤ 2 at study entry

Clinical Responders – n/N (%)	Stage I	Stage II
Crofelemer 125 mg*	5/18 (27.8)	10/42 (23.8)
Placebo	1/19 (5.2)	8/36 (22.2)

Source: Statistical Reviewer's analysis

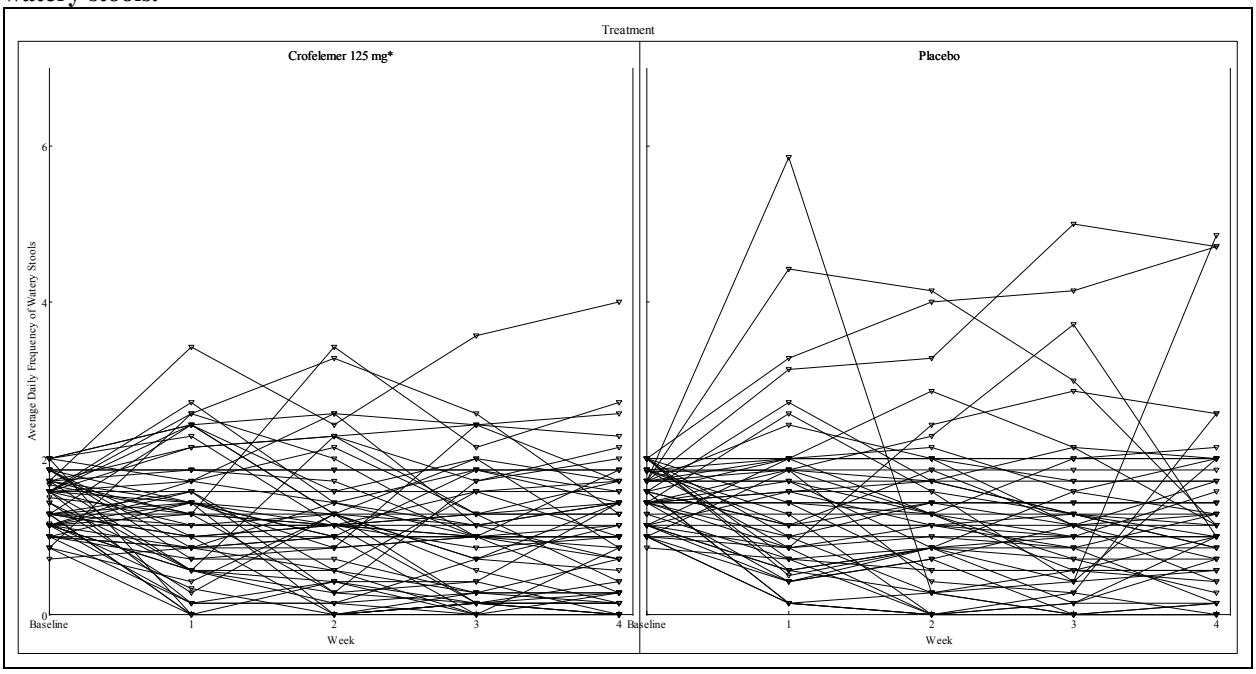
Table 16. Clinical response rates by study stage: subjects with baseline watery bowel movements > 2 at study entry

Clinical Responders – n/N (%)	Stage I	Stage II
Crofelemer 125 mg*	4/25 (16.0)	5/49 (10.2)
Placebo	0/31 (0.0)	2/52 (3.8)

Source: Statistical Reviewer's analysis

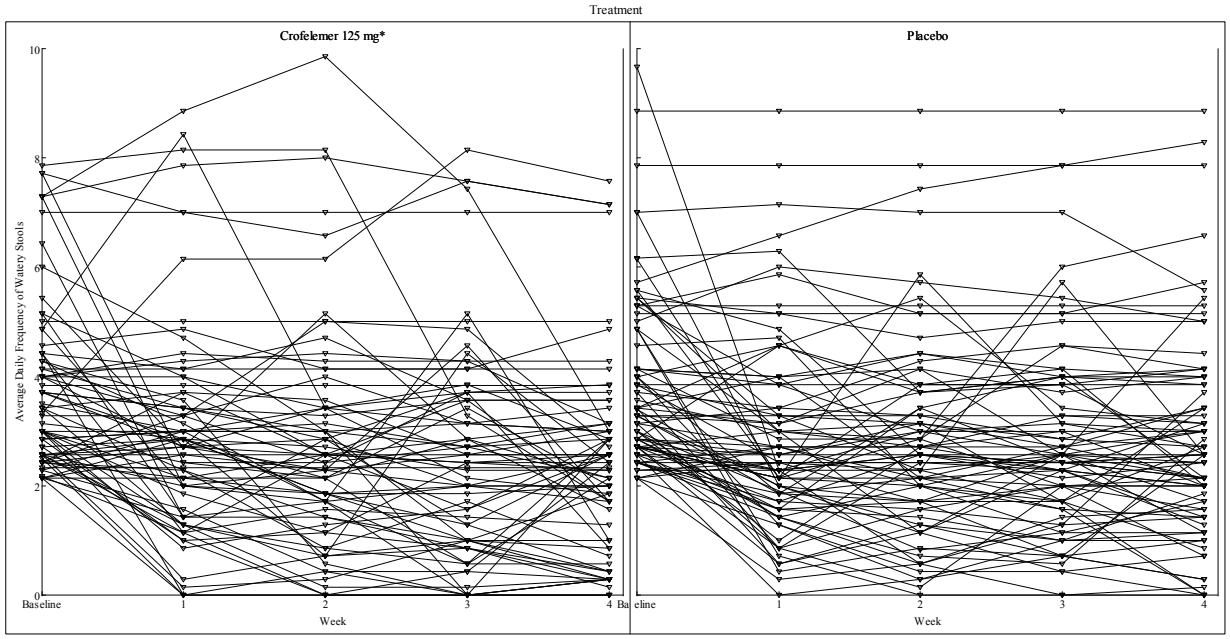
Inspection of graphs of the changes in number of watery bowel movements over time illustrates the differences in responses among the two subgroups. Those with ≤ 2 watery bowel movements at baseline (Figure 12) had much less variability over time than did subjects with >2 watery bowel movements at baseline (Figure 13).

Figure 12. Changes over time in the number of watery stools among subjects who had two or fewer baseline watery stools.



Source: Statistical Reviewer's analysis

Figure 13. Changes over time in the number of watery stools among subjects who had more than two baseline watery stools.



Source: Statistical Reviewer's analysis

3.2.4.3.5 Exploratory analyses of the relationship between manufacturing batches and response rates

The Botanical Review Team requested analyses to assess whether the clinical response of crofelemer-treated subjects was consistent across drug batches. However, analyses that are restricted to crofelemer-treated subjects only and that disregard the study design should be avoided. For example, because no single batch was studied in both stages, batch is confounded with study stage; see

Table 17. Therefore, for example, it is not possible to know whether the smaller treatment effect observed for Stage II can be attributed solely to an increase in the placebo response rate, as suggested by the Applicant, or because differences in manufacturing batches led to a crofelemer response rate that was lower than what may have been expected.

Table 17. Number of subjects receiving crofelemer 125 mg, by lot and stage

	Pooled Manufacturing Lots (Batches)							
STAGE	3059847R	3061308R/ 3061703R	3062741R/ 3062743R	3063506R/ 3063507R	3064439R/ 3064440R	3065503R/ 3065505R	3067354R/ 3067355R	TOTAL
I	2	7	13	14	9	1	-	46
II	-	-	-	-	-	-	92	92
								138

Source: Statistical Reviewer's analysis, using data submitted in ***Response to FDA Request for Information, response submitted 2/14/2012, Sequence 003***

Table 18. Number of subjects receiving placebo, by lot and stage

	Lot Number					
STAGE	3059686R	3063643R	3064434R	3070578R	3079606R	TOTAL
I	26	24	-	-	-	50
II	-	1	41	19	28	89
						139

Source: Statistical Reviewer's analysis, using data submitted in ***Response to FDA Request for Information, response submitted 2/14/2012, Sequence 003***

Appendix 6-3 contains graphical displays of each subject's changes over time in average daily watery bowel movement frequency. They are presented for study stage and lot for crofelemer 125 mg and for placebo treatment groups.

3.2.4.3.6 The clinical study report contains inconsistencies and lacks details

The clinical study report contained numerous inconsistencies and, in other instances, lacked sufficient detail needed for an efficient statistical review. Review areas that required extra time included the definition of the primary endpoint, footnotes to tables, and explanation of adaptation procedures. I discuss each of these here.

The clinical study report did not clearly define the primary endpoint, which resulted in misunderstandings among the clinical and statistical reviewers. For example, the clinical study report defines the primary endpoint as (for example, see clinical study report: page 56, Section 9.5.2 Efficacy Assessments and Endpoints; and page 63, Section 9.7.4 Analysis of Primary Endpoint):

The primary efficacy endpoint was the proportion of subjects in the Intent-to-Treat (ITT) population who experienced clinical response, which was defined as ≤ 2 watery bowel movements per week during at least 2 of the 4 weeks of the 4-week efficacy assessment period.

However, the protocol and the statistical analysis plan both stated that subjects who used anti-diarrheal or opiate pain medications for >3 days in the PC phase were non-responders. This definition was also included as footnotes to many tables contained in the clinical study report, and was the definition used in the statistical analyses.

The description of the adaptive design procedures was not precise or always accurate. For example, although the study report stated that Wald statistics were used for the pairwise comparisons, my review of the results and the SAS macro showed that asymptotic Pearson chi-square tests were used for the pairwise comparisons, and that one-sided Yule confidence intervals were calculated. For these reasons the footnotes contained in the tables that summarize the results for Stage I are incorrect. The p-values and confidence intervals reported for Stage I were not based on the Posch et al methodology.

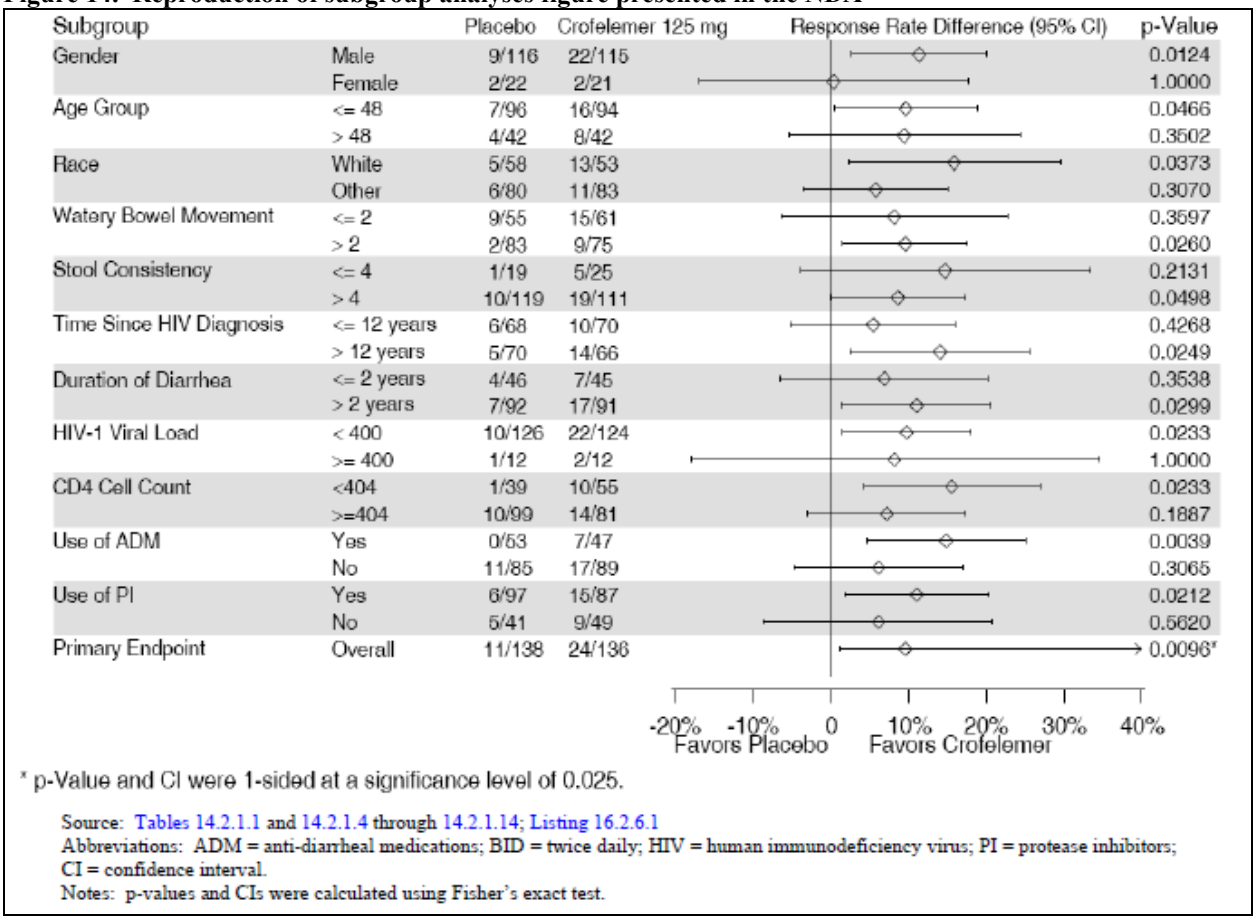
3.3 Evaluation of Safety

The Medical Division did not request any safety analyses. According to the medical reviewers, crofelemer appears to be well-tolerated with an acceptable adverse event profile.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The submission presents the results of subgroup analyses, as shown in the following figure:

Figure 14. Reproduction of subgroup analyses figure presented in the NDA



Subgroup		Placebo	Crofelemer 125 mg	p-Value
Gender	Male	9/116	22/115	0.0124
	Female	2/22	2/21	1.0000
Age Group	<= 48	7/96	16/94	0.0466
	> 48	4/42	8/42	0.3502
Race	White	5/58	13/53	0.0373
	Other	6/80	11/83	0.3070
Watery Bowel Movement	<= 2	9/55	15/61	0.3597
	> 2	2/83	9/75	0.0260
Stool Consistency	<= 4	1/19	5/25	0.2131
	> 4	10/119	19/111	0.0498
Time Since HIV Diagnosis	<= 12 years	6/68	10/70	0.4268
	> 12 years	5/70	14/66	0.0249
Duration of Diarrhea	<= 2 years	4/46	7/45	0.3538
	> 2 years	7/92	17/91	0.0299
HIV-1 Viral Load	< 400	10/126	22/124	0.0233
	>= 400	1/12	2/12	1.0000
CD4 Cell Count	<404	1/39	10/55	0.0233
	>=404	10/99	14/81	0.1887
Use of ADM	Yes	0/53	7/47	0.0039
	No	11/85	17/89	0.3065
Use of PI	Yes	6/97	15/87	0.0212
	No	5/41	9/49	0.5620
Primary Endpoint	Overall	11/138	24/136	0.0096*

* p-Value and CI were 1-sided at a significance level of 0.025.

Source: Tables 14.2.1.1 and 14.2.1.4 through 14.2.1.14; Listing 16.2.6.1
Abbreviations: ADM = anti-diarrheal medications; BID = twice daily; HIV = human immunodeficiency virus; PI = protease inhibitors; CI = confidence interval.
Notes: p-values and CIs were calculated using Fisher's exact test.

Statistical Reviewer's Note: With the exception of the primary endpoint, all p-values and confidence intervals are two-sided.
Source: Figure 8, Clinical Study Report

The submission also notes the largest treatment differences (>10%) in favor of crofelemer were in the following subgroups (see page 98 of the clinical study report). Note that these p-values are all two-sided and are not adjusted for multiple comparisons.

- White subjects (16%, p = 0.0373),
- CD4 count < 404 (16%, p = 0.0233),
- Daily stool consistency ≤ 4 (15%, p = 0.2131),
- ADM use in prior 4 weeks (15%, p = 0.0039),
- HIV diagnosis > 12 years (14%, p = 0.0249),
- Males (11%, p = 0.0124),
- Diarrhea duration > 2 years (11%, p = 0.0299), and

- Use of protease inhibitors (11%, p = 0.0212).

I do not agree with the Applicant's approach to analyzing the subgroups, which led to their conclusions that a statistically significant difference in one subgroup but not the other among several of the subgroup analyses (e.g., significant among those who used ADMs within four weeks prior to first dose; not significant among those who did not). Further, the analyses do not account for multiplicity or the study's adaptive design. The effect of ignoring stage of study on the interpretation of the results is unknown.

A more appropriate analysis is one that compares the treatment effect among the subgroups (e.g. the treatment effect among ADM use within four weeks prior to first dose vs. the treatment effect among those who did not use ADMs within four weeks). Using this approach, inspection of Figure 14 suggests there are no differences amongst the subgroups.

4.1 Gender, Race, Age, and Geographic Region

Female subjects had too few clinical responses (2/22 for placebo and 2/22 for crofelemer 125 mg) to conclude whether crofelemer is effective in women and whether the effect among female subjects is consistent with the effect among male subjects; see Figure 14. Further, the treatment effect did not appear to differ across the two age categories (<48 years, ≥48 years) that were defined by the Applicant.

The Applicant's assessment of efficacy among racial subgroups did not examine 'Black/African American' as its own category, even though the number of 'Black/African American subjects' who received either crofelemer 125 mg or placebo (n=104) was sufficient to allow an analysis for this subgroup only. Instead 'Black/African American' and 'Other' were combined together to form a single category. The number of 'Black/African American' subjects was about the same as the number of 'White/Caucasian' subjects (n=111) who received either crofelemer 125 mg or placebo. Relative to 'White/Caucasian' subjects who received crofelemer 250 mg or crofelemer 500 mg, 'Black/African American' subjects are under-represented in these two treatment groups because most 'Black/African American' subjects were enrolled in Stage II, primarily at Site #72 (see Section 3.2.2 of my review). The 'Other' category, which comprises mostly 'Hispanics', contains 58 subjects who received either crofelemer 125 mg or placebo.

The clinical response rates by treatment group for the race categories of 'Black/African American', 'White/Caucasian' and 'Hispanic' are shown in Table 19. There are too few subjects for meaningful comparisons among the remaining racial subgroups: American Indian: n=2; Asian/Pacific Islander: n=1; Italian[7]: n=1.

These results for the various race categories suggest that 'Black/African American' subjects did not derive a treatment benefit from crofelemer 125 mg, a finding that is consistent across study

[7] The clinical study report did not indicate why 'Italian' was not combined with one of the other standard racial subgroups.

stage. The suggestion of a lack of treatment benefit among 'Black/African American' subjects contrasts with the finding of a consistent treatment benefit among Hispanic subjects (14.8) and among White/Caucasian subjects (15.9). Although not shown in the table below, the size of the treatment effect for 'Black/African American' subjects differs from the combination of Hispanic and White/Caucasian subjects (95% confidence interval: [6%, 26%]).

Table 19. Clinical response rates by treatment group and race.

		Crofelemer 125 mg*	Crofelemer 250 mg	Crofelemer 500 mg	Placebo
Black/African American:	N	51	9	9	53
	Clinical Response Rate (%) Treatment Effect Size 95% confidence interval	7.8 -1.6 [-13, 10]	22.2 12.8	11.1 1.7	9.4 -
White/Caucasian:	N	53	34	26	58
	Clinical Response Rate Treatment Effect Size 95% confidence interval	24.5 15.9 [2.2, 30]	8.8 .2	19.2 10.61	8.6 -
Hispanic	N	32	10	12	25
	Clinical Response Rate Treatment Effect Size 95% confidence interval	18.8 14.8 [-3.3, 32.3]	0.0 -4.0	25.0 21.0	4.0 -

Note: the confidence intervals are exact confidence intervals on the difference in proportions, calculated using EXACT. The analyses do not account for study stage.
Source: Statistical Reviewer's analysis

In response to an FDA Request for Information[8], the Applicant asserted "the apparent lack of treatment effect among Black/African American subjects is likely due to the higher percentage of those subjects having less severe diarrhea at baseline compared with subjects of other races." However, when clinical response rates are calculated by race and by baseline watery bowel movements, the sizes for the treatment effect among 'Black/African American' subjects is negative for those with ≤2 baseline watery bowel movements (-6.7%) and negligible for those with >2 baseline watery bowel movements (3.4%), see Table 20. By contrast the size of the treatment effect for all other subjects was 17% for those with ≤2 baseline watery bowel movements and 13% for those with >2 baseline watery bowel movements.

[8] Response to FDA Request for Information, response submitted 9/12/2012, Sequence 032

Table 20. Clinical response by race and by baseline watery bowel movements

Race Group	Baseline Weekly Watery Bowel Movements	Placebo	Crofelemer 125 mg*
Black / African American	≤ 2	4 / 26 (15.4%)	2 / 23 (8.7%)
	> 2	1 / 27 (3.7%)	2 / 28 (7.1%)
Other	≤ 2	5 / 29 (17.2%)	13 / 38 (34.2%)
	> 2	1 / 56 (1.8%)	7 / 47 (14.9%)

Source: IR10 Table 2

Source: Table 2 in Response to FDA Request for Information, response submitted 9/12/2012, Sequence 032

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The statistical evidence to support the desired indication for crofelemer, "the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy", is modest. The primary evidence comes from a single study called the ADVENT Trial. Although the difference between the clinical response rates for crofelemer 125 mg (18%) and placebo (8%) is statistically significant at α=0.025 (p-value = 0.01, one-sided) with a one-sided 97.5% confidence interval of [1.2%, ∞], the 10% treatment effect size is not consistent across important study design attributes, including stage of study and study sites. Further, the within group clinical response rate of 18% for crofelemer 125 mg is relatively low.

ADVENT was a two-stage adaptive design study. Subjects who enrolled in Stage I were randomized to one of three crofelemer doses (125 mg, 250 mg, 500 mg) or placebo. Each treatment group had approximately 50 subjects. Based on the results of an interim analysis, the 125 mg dose was selected for further study in Stage II. Therefore, subjects who enrolled in Stage II were randomized to either 125 mg (n=92) or placebo (n=88). All subjects had the option of enrolling in a five month, placebo-free, open-label, follow-up period.

Notably, the treatment effect was not consistent across study stage and was statistically significant for Stage I only, despite a larger sample size in Stage II; see Table 7 and Table 8 of my review. The size of the Stage I treatment effect (18%; p=.0019, one-sided) was larger than the size of the Stage II treatment effect (5%; p=.1690, one-sided). The Applicant explained this difference by noting (1) that crofelemer had a more profound treatment effect in subjects with more clinically significant diarrhea and (2) that the Stage II placebo subjects had more clinically

significant diarrhea as assessed by the number of watery stools at baseline than did the Stage I placebo subjects. Therefore, they asserted, the difference was likely due to the imbalance between stages in clinically significant diarrhea among the placebo-treated subjects. My review, however, suggests the imbalance may be due to two placebo-treated subjects who had unusually high baseline values of watery stools. In addition, the point estimate of the treatment effect for subjects with less severe diarrhea was comparable to the point estimate of the treatment effect for subjects with more severe diarrhea.

Further, the treatment effect was not consistent across study sites. The largest study site (n=36) did not show any treatment effect, with only one responder in the crofelemer 125 mg treatment group and only one responder in the placebo treatment group.

Based on the relatively small numbers of clinical responders who entered the placebo-free phase, the results suggest a reasonable number of the crofelemer 125 mg responders maintained their response. Of the crofelemer 125 mg responders (n=22) who entered the placebo-free phase, 14 were responders through every month of the PF phase. However, this result needs to be balanced by the finding that 5 lost their response to treatment by Month 3 of the placebo-free phase.

The Botanical Review Team requested analyses to assess whether the clinical response of crofelemer-treated subjects and crofelemer batch were related. Although the clinical response rates appear similar across batches, this analysis is simplistic and can not be relied upon to give conclusions that are reliable. An appropriate analysis needs to consider the study design features and the clinical response rates among concurrent placebo controls. For example, one batch was used in Stage II only and not in Stage I. Because this batch was not used in Stage I, we are unable to assess whether difference in the treatment effect size between stages is due to batches or the study design.

The ADVENT trial also illustrates perils that may occur when two-stage adaptive designs are used for Phase 3 studies. If the rules for selecting a dose permitted stopping the study for futility at the interim analysis, the dose selection meeting minutes suggest the interim analysis committee may have recommended stopping the study due to the lack of a meaningful difference in the clinical response rates among the treatment groups. However, the response rates calculated at the interim analysis differed from those used in the final analysis of the study results, resulting in an underestimate by the interim analysis of the difference between the response rates for crofelemer 125 mg and placebo at the interim analysis: 8% at the interim vs. 18% for the final. Two reasons accounted for this difference. First, the consulting statistician who did the interim analysis mistakenly included data from the post-randomization three-day run-in period in his calculation of response rates instead of excluding these days as stipulated in the protocol. Second, the sources of data used to define clinical non-responders differed between the two analyses. At the interim analysis, only the daily diary data were used to determine the use of anti-diarrheal medications and opiates. The final analysis used an additional data source – the electronic case report form. Taken together, these two reasons changed the response rates in a way that increased the treatment effect seen for Stage I. Had a futility rule been in place at the time of the interim analysis, the study may have been stopped needlessly.

5.2 Conclusions and Recommendations

The statistical evidence to support the desired indication for crofelemer, "the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy", is modest. The primary evidence comes from a single study called the ADVENT Trial. Although the difference between the clinical response rates for crofelemer 125 mg (18%) and placebo (8%) is statistically significant at α=0.025 (p-value = 0.01, one-sided) with a one-sided 97.5% confidence interval of [1.2%, ∞], the 10% treatment effect size is not consistent across important study design attributes, including stage of study and study sites. Further, the within group clinical response rate of 18% for crofelemer 125 mg is relatively low.

6 APPENDICES

Appendix 6-1

Response from Applicant to Information Requested on March 5, 2012

The response includes:

- Formula for the Wald statistic used to compare treatment with placebo
- SAS code used to calculate p-values and confidence intervals for the primary endpoint in ADVENT
- A statement on the validity of the SAS code

Information Requested on March 5, 2012

Please provide the SAS code that was used to calculate, based on the methods of Posch and Bauer, the p-values and confidence intervals for Study NP303-101 (ADVENT).

State whether this code is the same code used to generate the simulation results that were submitted in 2007 or if this code is different. Describe any differences.

The code (closetest.sas, a macro) that was used to calculate the p-values and confidence intervals for final analysis in Study NP303-101 (ADVENT) was written in SAS by Salix. The code used to generate the simulation results that were submitted in 2007 was written in C and inserted into Excel as a dynamic linked library (dll) by (b) (4) Both codes were based on the methods of Posch and Bauer.

The formula below, used to calculate the Wald statistics for the pair-wise comparisons of each crofelemer dose versus placebo, was the same for both interim analysis (Page 2 of Interim Analysis Report; the interim analysis was conducted by (b) (4) and final analysis (Final analysis was conducted by Salix).

(b) (4)

With the SAS code for final analysis, Salix could reproduce the adjusted overall p-values and adjusted 1-sided 97.5% confidence interval in the example of Section 6.2 in Posch and Bauer's publication (included as Attachment C in the NP303-101 SAP). The example had a similar study design as NP303-101.

The SAS code for generating the primary efficacy tables is teff.sas which used the SAS code (closetest.sas).

Source: Response from Applicant to Information Requested on March 5, 2012; response submitted 3/15/2012, Sequence 006

The following is the SAS macro submitted by the applicant as part of "*Response from Applicant to Information Requested on March 5, 2012*"

(b) (4)

[redacted]

2 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

Appendix 6-2

Response from Applicant to Information Requested on July 5, 2012

Response to FDA Request for Information, response submitted 7/13/2012, Sequence 018

IR8 Table 2
Number and Percentage of First-Time Clinical Responders by Week
Population: Placebo Subjects Crossed-Over to Crofelemer 125 mg and Crofelemer 125 mg Subjects

	Responders		First Time Responders	
	Placebo -> Crofelemer 125 mg	Crofelemer 125 mg -> Crofelemer 125 mg	Placebo -> Crofelemer 125 mg	Crofelemer 125 mg* -> Crofelemer 125 mg
Placebo-Controlled Phase				
Week 1	5/99 (5.1%)	13/136 (9.6%)	5/99 (5.1%)	13/136 (9.6%)
Week 2	9/99 (9.1%)	18/136 (13.2%)	5/99 (5.1%)	9/136 (6.6%)
Week 3	12/99 (12.1%)	24/136 (17.6%)	5/99 (5.1%)	9/136 (6.6%)
Week 4	11/99 (11.1%)	25/136 (18.4%)	5/99 (5.1%)	5/136 (3.7%)
Placebo-Free Extesion Phase				
Week 1	27/99 (27.3%)	34/121 (28.1%)	17/99 (17.2%)	13/121 (10.7%)
Week 2	31/99 (31.3%)	41/121 (33.9%)	7/99 (7.1%)	11/121 (9.1%)
Week 3	29/99 (29.3%)	43/121 (35.5%)	3/99 (3.0%)	10/121 (8.3%)
Week 4	29/99 (29.3%)	49/121 (40.5%)	3/99 (3.0%)	5/121 (4.1%)
Week 5	35/99 (35.4%)	46/121 (38.0%)	4/99 (4.0%)	2/121 (1.7%)
Week 6	35/99 (35.4%)	53/121 (43.8%)	6/99 (6.1%)	7/121 (5.8%)
Week 7	38/99 (38.4%)	54/121 (44.6%)	4/99 (4.0%)	2/121 (1.7%)
Week 8	40/99 (40.4%)	55/121 (45.5%)	3/99 (3.0%)	4/121 (3.3%)
Week 9	43/99 (43.4%)	55/121 (45.5%)	0	3/121 (2.5%)
Week 10	45/99 (45.5%)	57/121 (47.1%)	0	1/121 (0.8%)
Week 11	42/99 (42.4%)	53/121 (43.8%)	0	1/121 (0.8%)
Week 12	42/99 (42.4%)	50/121 (41.3%)	2/99 (2.0%)	0
Week 13	42/99 (42.4%)	53/121 (43.8%)	1/99 (1.0%)	0

Note: Clinical response in a week was defined as <-2 watery stools during a given week. If a subject used an anti-diarrhea medication (ADM) or opiate pain medication for greater than 3 days (consecutive or non-consecutive) during a specific month, the subject was classified as non-responder for all four weeks in that month. A subject who had a missing week or terminated early from study, the subject was classified as non-responder for the specific missing week and the weeks after drop-out.

Program: TFWKRSP.sas Run: 12JUL2012 15:20, Dataset: EFFWK Created: 20MAY11:14:34:40

IR8 Table 2
Number and Percentage of First-Time Clinical Responders by Week
Population: Placebo Subjects Crossed-Over to Crofelemer 125 mg and Crofelemer 125 mg Subjects

	Responders		First Time Responders	
	Placebo -> Crofelemer 125 mg	Crofelemer 125 mg -> Crofelemer 125 mg	Placebo -> Crofelemer 125 mg	Crofelemer 125 mg* -> Crofelemer 125 mg
Placebo-Controlled Phase				
Week 1	5/99 (5.1%)	13/136 (9.6%)	5/99 (5.1%)	13/136 (9.6%)
Week 2	9/99 (9.1%)	18/136 (13.2%)	5/99 (5.1%)	9/136 (6.6%)
Week 3	12/99 (12.1%)	24/136 (17.6%)	5/99 (5.1%)	9/136 (6.6%)
Week 4	11/99 (11.1%)	25/136 (18.4%)	5/99 (5.1%)	5/136 (3.7%)
Placebo-Free Extesion Phase				
Week 1	27/99 (27.3%)	34/121 (28.1%)	17/99 (17.2%)	13/121 (10.7%)
Week 2	31/99 (31.3%)	41/121 (33.9%)	7/99 (7.1%)	11/121 (9.1%)
Week 3	29/99 (29.3%)	43/121 (35.5%)	3/99 (3.0%)	10/121 (8.3%)
Week 4	29/99 (29.3%)	49/121 (40.5%)	3/99 (3.0%)	5/121 (4.1%)
Week 5	35/99 (35.4%)	46/121 (38.0%)	4/99 (4.0%)	2/121 (1.7%)
Week 6	35/99 (35.4%)	53/121 (43.8%)	6/99 (6.1%)	7/121 (5.8%)
Week 7	38/99 (38.4%)	54/121 (44.6%)	4/99 (4.0%)	2/121 (1.7%)
Week 8	40/99 (40.4%)	55/121 (45.5%)	3/99 (3.0%)	4/121 (3.3%)
Week 9	43/99 (43.4%)	55/121 (45.5%)	0	3/121 (2.5%)
Week 10	45/99 (45.5%)	57/121 (47.1%)	0	1/121 (0.8%)
Week 11	42/99 (42.4%)	53/121 (43.8%)	0	1/121 (0.8%)
Week 12	42/99 (42.4%)	50/121 (41.3%)	2/99 (2.0%)	0
Week 13	42/99 (42.4%)	53/121 (43.8%)	1/99 (1.0%)	0

Note: Clinical response in a week was defined as <-2 watery stools during a given week. If a subject used an anti-diarrhea medication (ADM) or opiate pain medication for greater than 3 days (consecutive or non-consecutive) during a specific month, the subject was classified as non-responder for all four weeks in that month. A subject who had a missing week or terminated early from study, the subject was classified as non-responder for the specific missing week and the weeks after drop-out.

Program: TFWKRSP.sas Run: 12JUL2012 15:20, Dataset: EFFWK Created: 20MAY11:14:34:40

IR8 Table 2
Number and Percentage of First-Time Clinical Responders by Week
Population: Placebo Subjects Crossed-Over to Crofelemer 125 mg and Crofelemer 125 mg Subjects

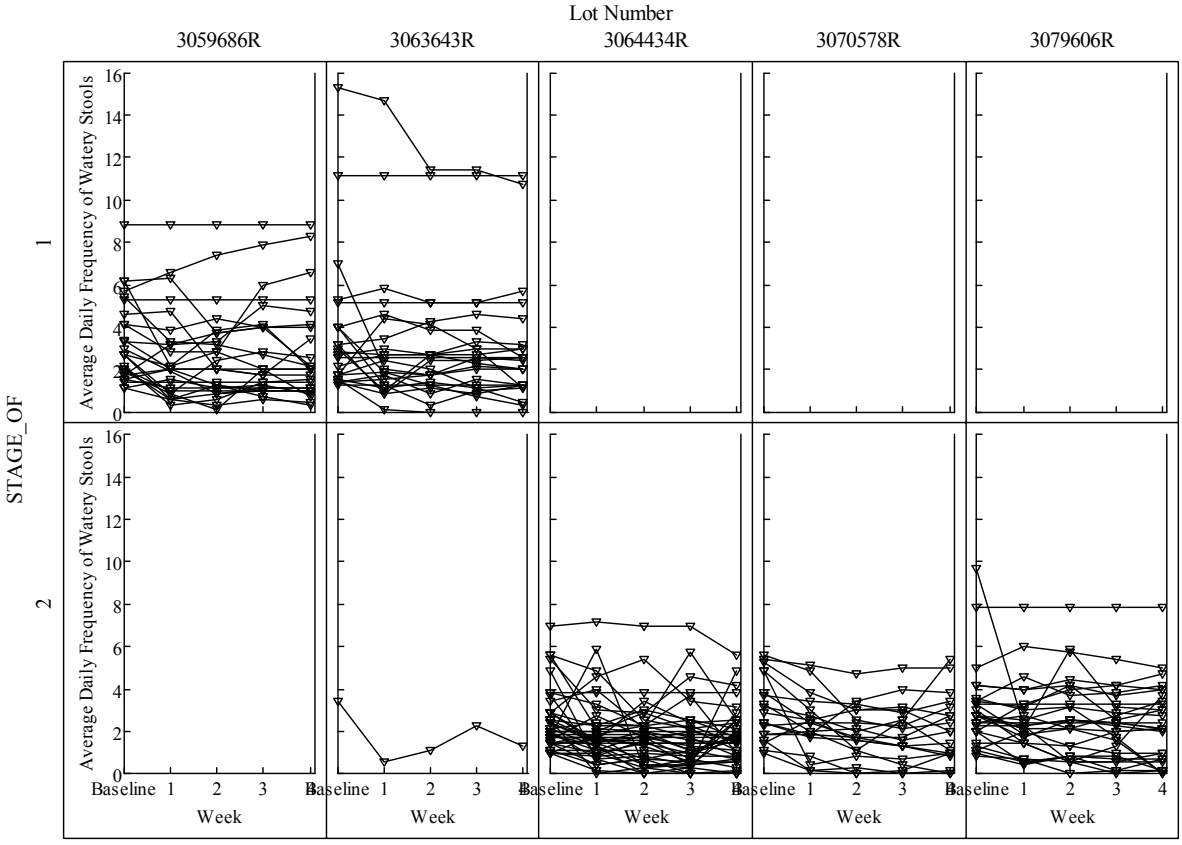
	Responders		First Time Responders	
	Placebo -> Crofelemer 125 mg	Crofelemer 125 mg -> Crofelemer 125 mg	Placebo -> Crofelemer 125 mg	Crofelemer 125 mg* -> Crofelemer 125 mg
Week 14	40/99 (40.4%)	50/121 (41.3%)	0	1/121 (0.8%)
Week 15	41/99 (41.4%)	54/121 (44.6%)	0	0
Week 16	43/99 (43.4%)	52/121 (43.0%)	1/99 (1.0%)	0
Week 17	40/99 (40.4%)	52/121 (43.0%)	0	0
Week 18	40/99 (40.4%)	57/121 (47.1%)	0	2/121 (1.7%)
Week 19	44/99 (44.4%)	56/121 (46.3%)	0	0
Week 20	33/99 (33.3%)	38/121 (31.4%)	0	0

Note: Clinical response in a week was defined as <-2 watery stools during a given week. If a subject used an anti-diarrhea medication (ADM) or opiate pain medication for greater than 3 days (consecutive or non-consecutive) during a specific month, the subject was classified as non-responder for all four weeks in that month. A subject who had a missing

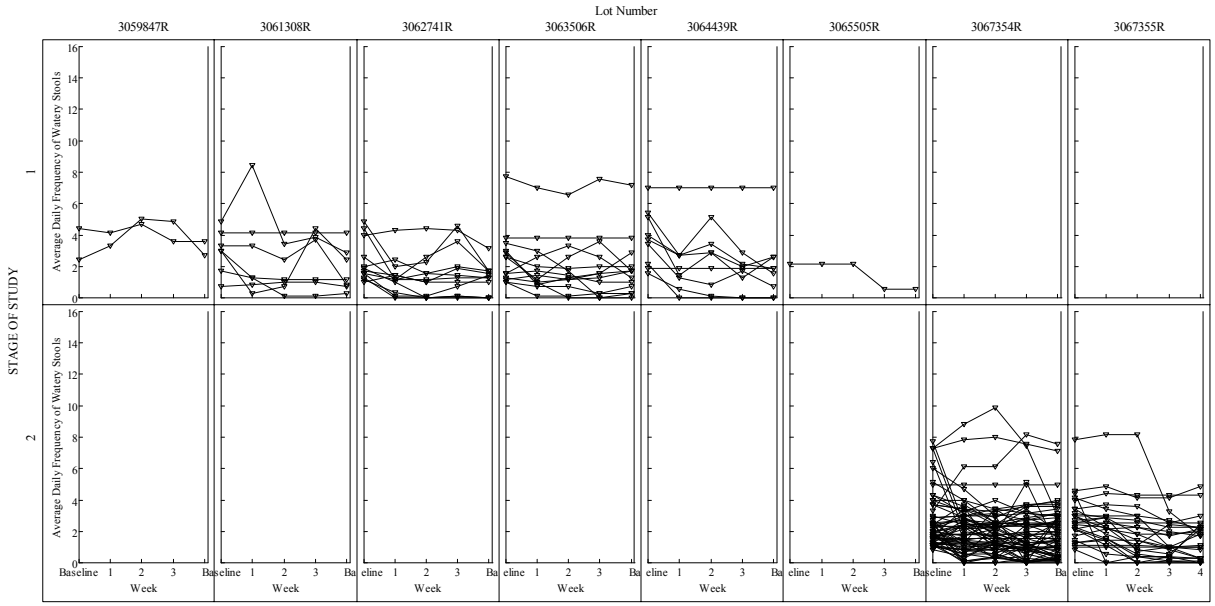
Appendix 6-3

Patient Profiles: Average Daily Frequency of Watery Stools vs Week, by Lot Number and Stage of Study and by Treatment Group

Placebo: Average Daily Frequency of Watery Stools vs. Week, by Lot Number and Stage of Study



Crofelemer 125 mg Average Daily Frequency of Watery Stools vs. Week, by Lot Number and Stage of Study



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/s/

LISA A KAMMERMAN
12/17/2012

MICHAEL E WELCH
12/18/2012
Concur with review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202292 **Applicant: Salix Pharmaceuticals, Inc.** **Stamp Date: 12/5/2011**

Drug Name: Crofelemer Tablets, 125 mg **NDA/BLA Type: Priority**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	Yes			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Yes			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	Yes (see comments)			**Efficacy:** Reported for ADVENT. Reported for the pooled results from the other two studies – see ISE. **Safety:** In ISS only; not in study reports
4	Data sets in EDR are accessible and they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	Yes			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

Tabular listing of the three efficacy studies:

Study Number	Study Design/Crofelemer Regimen/ Control Regimen	Duration	Subject Population
NP303-101 (ADVENT)	Double-blind, placebo-controlled, 2-stage, adaptive design, phase 3 study • Crofelemer 125 mg BID tablets (n=136)[a] • Crofelemer 250 mg BID tablets (n=54)[a] • Crofelemer 500 mg BID tablets (n=46)[a] • Placebo BID tablets (n=138)[a]	4 weeks of PC treatment; 20 weeks of PF treatment	HIV+ subjects on stable ART with ≥ 1 month history of diarrhea
37554-210	Double-blind, placebo-controlled, phase 3 study • Crofelemer 250 mg QID tablets (n=102) • Crofelemer 500 mg QID tablets (n=100) • Crofelemer 500 mg QID beads (n=100) • Placebo QID (n=98)	6 days of inpatient treatment; 21 days of outpatient treatment	HIV/AIDS subjects on stable treatment regimen for AIDS with ≥ 14 day history of diarrhea
37554-209	Double-blind, placebo-controlled, phase 2 study • Crofelemer 500 mg QID beads (n=43) • Placebo QID (n=42)	4 days of inpatient treatment	HIV/AIDS subjects on stable treatment regimen for AIDS with diarrhea

Abbreviations: HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome; PC = placebo-controlled; PF = placebo-free; BID = twice daily; QID = 4 times daily; and ART = antiretroviral therapy.

a Number of subjects in the PC treatment phase.

Source: Table 1, Clinical Overview of the NDA

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				Under review
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	See comment			For the adaptive design of ADVENT, I see the IAC (independent analysis committee) charter and the interim analysis report (Section 16.1.9.4, also called 'Dose Selection Report' on page 94 of CSR). I don't see the meeting minutes where dose selection was discussed.
Appropriate references for novel statistical methodology (if present) are included.	Yes			Adaptive design
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		No		For the AE.xpt files: Variable names and definitions differ across the three studies.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				Primary endpoint accounts for discontinuations. A per protocol analysis appears to be the only analysis looking at the effect of missing data. Will need to examine this in the statistical review.

Please include the following comment in the 74-Day Letter:

1. Please identify the location of the minutes for the independent analysis committee meeting that was convened for the ADVENT trial. We note the submission contains an "Interim Analysis Report" in Appendix 16.1.9.4. However, we are looking for the minutes that describe the discussion surrounding the dose that was selected for the second phase of the study.

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

LISA A KAMMERMAN
02/09/2012

MICHAEL E WELCH
02/09/2012