CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	August 31, 2012
Established Name	Crofelemer
(Proposed) Trade Name	Fulyzaq, 125 mg tablets
Therapeutic Class	Antidiarrheal Product
Applicant	Salix Pharmaceuticals, Inc
Formulation(s)	For oral administration
Dosing Regimen	125 mg tablet orally twice daily
Indication(s)	Control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy
Intended Population(s)	Patients with HIV/AIDS on anti-retroviral therapy

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant Salix Pharmaceuticals submitted this original NDA for the indication of control and symptomatic relief of diarrhea in patients ages 18 years and over with HIV/AIDS on anti-retroviral therapy.

This review primarily assesses the efficacy and safety of a randomized, double-blind, placebo-controlled (four weeks) and placebo-free (twenty weeks), multi-center clinical study (NP 303-101; ADVENT) (n=376) in HIV positive patients on stable anti-retroviral therapy (ART) with a history of diarrhea for one month or more. Diarrhea was defined as either persistently loose stools despite regular use of antidiarrheal medication (ADM) (e.g., loperamide, diphenoxylate, and bismuth subsalicylate) or one or more watery bowel movements (BMs) per day without regular ADM use.

The study had a two-stage adaptive design. Each stage enrolled patients separately; however, the dose for the second stage was selected based on an interim analysis of data from the first stage. In the first stage, patients were randomized 1:1:1:1 to one of three Crofelemer dose regimens (125, 250, or 500 mg bid) or placebo. In the second stage, patients were randomized 1:1 to Crofelemer 125 mg bid or placebo. In the 20-week placebo-free (PF) phase of each of the stages, patients treated with Crofelemer in the PC phase continued the same dose; patients treated with placebo were re-randomized to one of the Crofelemer dose regimens.

In the PC phase, 136 patients received Crofelemer 125 mg bid, 54 patients received 250 mg bid, 47 patients received 500 mg bid, and 138 patients received placebo. In the PF phase, 220 patients were treated with Crofelemer 125 mg bid, 67 patients were treated with 250 mg bid, and 50 patients were treated with 500 mg bid.

The primary efficacy analysis was based on demonstration of clinical response in the PC phase. Clinical response was defined as ≤ 2 watery bowel movements per week for at least 2 of 4 weeks during the 4-week efficacy assessment periods. The results show that a larger proportion of patients in the Crofelemer 125 mg bid group achieved clinical response as compared with the placebo group (17.6% vs. 8.0%, p = 0.0096; one-sided compared with alpha 0.025). Given that patients were required to report at least 5 days of watery bowel movements during the last 7 days of the Screening phase to be randomized into the study, ≤ 2 watery bowel movements per week represented an improvement from baseline for at least 50% of the time.

This review also discusses exploratory subgroup analyses of the ADVENT study using Fisher's exact test. The purpose of the analyses is to identify the responsive subgroups

to Crofelemer treatment. The p-value served as a guide to identify the responsive subgroups as compared with the placebo. It is not intended for a formal statistical conclusion.

Results of the exploratory subgroup analyses are summarized below.

- The subgroup of patients with persistent diarrhea despite the use of prior ADMs had a higher treatment difference (Crofelemer 125 mg bid vs. placebo) for the primary endpoint (clinical response) than the subgroup of patients who had no prior use of ADMs (treatment difference of 14.6% in the subgroup with any prior ADM use vs. 1.9% in the subgroup with no prior ADM use).

  It should be noted that the treatment difference observed in the subgroup of patients who used 1 ADM, compared with the subgroup of patients who used 2 or more ADMs, in an attempt to control diarrhea and failed during the 4-weeks prior to the study, was 6.9% and 27.6%, respectively.

- The subgroup of patients with concomitant protease inhibitor (PI) use and persistent watery diarrhea had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients with no concomitant PI use (11.0% vs. 6.2%).

- The subgroup of patients with CD4 cell counts < 404 cells/mm^3 had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients with CD4 cell counts ≥ 404 cells/mm^3 (15.6% vs. 7.2%).

- The subgroup of patients with > 2 watery BM's per day had a similar treatment difference for the primary endpoint (clinical response) as the subgroup of patients with ≤ 2 watery BM's per day (9.6% vs. 8.2%).

- The subgroup of patients with duration of diarrhea > 2 years had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients with duration of diarrhea ≤ 2 years (11.1% vs. 6.9%).

- The subgroup of patients that had been diagnosed with HIV for > 12 years had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients that had been diagnosed with HIV for ≤ 12 years (14.1% vs. 5.5%).

In the 20-week PF phase, both the patients that crossed over from placebo and the patients that continued on Crofelemer appeared to show a persistent anti-diarrheal effect.

Taken together, the exploratory subgroup analyses and the results of the PF phase support the finding that Crofelemer treatment may address the unmet medical needs of HIV/AIDS patients.

In addition, there is supportive data from two studies (37554-210 and 37554-209) using a different formulation and a different primary endpoint (change from baseline in daily stool weight during the in-patient periods; Crofelemer N = 345 vs. Placebo N = 140). The results were supportive to Study ADVENT.

Because the control of diarrhea not only improves the quality of patients' lives, but also may improve the compliance to anti-retroviral therapy, these improvements are considered by the reviewer to be clinically relevant. Thus, Crofelemer may address the unmet medical needs in HIV diarrhea patients that are using anti-retroviral therapy.

Crofelemer had minimal systemic absorption as indicated by low plasma concentration in the ADVENT trial. A favorable safety profile was found from this study. The most frequent treatment-emergent adverse events (TEAEs) occurred in the Infections and Infestations (all Crofelemer: 10% vs. placebo: 11%) and Gastrointestinal Disorders (all Crofelemer: 9% vs. placebo: 6%) system organ classes. No deaths or non-fatal serous adverse events (SAEs) were considered drug related. No discontinuations were due to drug treatment. No ECG signals suggested a cardiac safety risk in the treated group. There was no evidence to suggest that Crofelemer had an effect on HIV status or anti-retroviral therapy. The integrated HIV safety database (696 patients) was also reviewed. The results were consistent with that of ADVENT.

In conclusion, this Clinical Reviewer recommends Approval for this NDA submission of Crofelemer for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.

1.2 Risk Benefit Assessment

Unmet Medical Need and Benefit:

- **Novel mechanism of action:** To date, there is no approved anti-HIV-diarrheal therapy. Loperamide and lomotil are used off-label for treating HIV diarrhea. Tolerance develops with repeated use. Treatment failure is primarily due to: (1) induction of hepatic metabolism enzymes (for conjugation with glucuronic acid), and (2) desensitization of opioid receptors on the surface of target cells. In contrast, Crofelemer action at luminal sites of the intestine blocks chloride channels. The direct anti-diarrhea action is not affected by hepatic enzymes or receptor desensitization. Thus, treatment of persistent and refractory HIV diarrhea with Crofelemer becomes possible.

- **HIV secretory diarrhea:** Over 50% of HIV infected patients have diarrhea during the course of their disease. There are at least four etiologies of HIV associated diarrhea: opportunistic infection diarrhea, HIV enterocolitis diarrhea, HAART (highly active anti-retroviral therapy) associated diarrhea, and Kaposi's sarcoma associated diarrhea. All of these may cause secretory diarrhea. Crofelemer is an inhibitor of two intestinal chloride channels that mediate the secretory diarrhea.

- **Anti-retroviral therapy associated diarrhea:** 40% of patients receiving HAART have moderate to severe diarrhea. 30% of patients receiving protease inhibitors have drug induced diarrhea. 28% of patients discontinue HAART due to GI intolerance. Treatment of refractory diarrhea may improve patient adherence to HAART.

- **Results of Study ADVENT:** The primary analysis demonstrated a statistically significant treatment difference for the primary endpoint of clinical response. Exploratory subgroup analyses using the primary endpoint of clinical response showed the following: (1) a higher treatment difference in the subgroup with prior ADM use than the subgroup with no prior ADM use; (2) a numerically higher treatment difference in the subgroup with concomitant PI use than the subgroup without concomitant PI use; (3) a numerically higher treatment difference in the subgroup with CD4 cell count < 404 cells/mm^3 than the subgroup with CD4 cell count ≥ 404 cells/mm^3; (4) a numerically higher treatment difference in the subgroup with duration of diarrhea > 2 years than the subgroup with duration of diarrhea ≤ 2 years; (5) a numerically higher treatment difference in the subgroup diagnosed with HIV for > 12 years than the subgroup diagnosed with HIV for ≤ 12 years. The 20-week PF phase showed a persistent anti-diarrheal effect.

Risks:

- A key risk of Crofelemer is that symptomatic treatment of diarrhea may delay the diagnosis and treatment of pathogen-specific infectious diarrhea. This risk will be addressed through addition of a statement in the Warnings and Precautions section of the labeling explaining this risk and recommending that infectious etiologies of diarrhea should be ruled out before starting Crofelemer.
- Reported AEs included musculoskeletal pain, dyspepsia, and constipation

In summary, in this reviewer's opinion, the above benefit-risk assessment is in favor of the approval of Crofelemer for the treatment of non-infectious diarrhea in patients with HIV/AIDS on anti-retroviral therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no recommendation for postmarket risk evaluation and mitigation.

1.4 Recommendations for Postmarket Requirements and Commitments

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric Postmarketing Requirements:

The pediatric plan of Crofelemer should evaluate pharmacokinetics (PK), efficacy and safety with different doses over a four week period in pediatric patients ages 1 month to 17 years. (b) (4)

DGIEP grants a partial waiver in pediatric patients ages birth to 4 weeks of age, because studies would be impossible or highly impractical; the clinical endpoints in the lowest age group would be impossible to meet because very few infants are treated with HIV medications.

Studies in pediatric patients 1 month to 17 years of age for the treatment of HIV-associated diarrhea was recommended as a deferral. The final study reports should be submitted to the Agency no latter than 5 years following the approval of the NDA. The Pediatric Research Committee (PeRC) PREA Subcommittee reviewed and agreed on July 25, 2012.

2 Introduction and Regulatory Background

2.1 Product Information

The product of the application is Crofelemer (also known as NP303 or SP-303). It is a naturally-occurring, oral anti-diarrheal agent prepared by isolation from the latex sap of the plant *Croton lechleri* of the family *Euphorbiaceae.* These species exist in the western Amazon regions of South America. Crofelemer is an extract of proanthrocyanidin oligomer with an average molecular weight range of 1100 – 2900

Dalton. The oligomer consists of 5 to 11 linearly linked monomers; (+)-gallocatechin and (-)-epigallocatechin are predominant monomers.

Crofelemer is a first-in-class gastrointestinal (GI) agent. In vitro and in vivo studies demonstrate that Crofelemer is an inhibitor of both the cAMP stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel and the calcium-activated chloride channels (CaCC) (Fischer, 2004; Tradtrantip, 2010). The CFTR chloride channel and CaCC regulate chloride and fluid secretion by intestinal epithelial cells (Field, 2003). The inhibition taking place at the luminal site of intestinal epithelium blocks chloride secretion in diarrhea and accompanying high volume water loss. As a result, Crofelemer treatment normalizes the flow of chloride ions and water in the GI tract.

Crofelemer has demonstrated in vitro activity against chloride secretion from exposure to cholera toxin (CT), forskolin, and *Escherichia coli* (*E. coli*) LT (*E. coli* heat labile toxin) or STa (*E. coli* heat stable toxin) toxins. Crofelemer also normalized electrolyte and fluid accumulation in vivo in CT-treated mice via its effects on intestinal prosecretory chloride channels (Crutchley, 2010; Gabriel, 1999; Tradtrantip, 2010).

During the development of Crofelemer, several formulations and multiple strengths of drug product have been used in clinical studies. Oral solutions of the powdered drug substance were used in early Phase 1 tolerance and pharmacokinetic studies. Subsequently, delayed-release solid oral dosage forms (enteric-coated beads and tablets) were developed and used in Phase 1, 2, and 3 clinical studies. The proposed commercial formulation was used in the pivotal Phase 3 study (NP303-101 or ADVENT). Patheon Pharmaceuticals Inc. (Patheon) was the manufacturer of the proposed commercial formulation for Crofelemer Tablets, 125 mg.

In this original NDA, the Applicant intended to demonstrate the efficacy and safety of Crofelemer in the treatment of HIV associated diarrhea.

2.2 Currently Available Treatments for Proposed Indications

To date, there is no approved therapy for HIV diarrhea. Anti-diarrhea agents (opioids), loperamide and lomotile, are used off-label. None of these provide sustained treatment effects. Their adverse reactions prevent long-term use.

A) Loperamide
Trade name: Loperamide Softgel
Generic name: Loperamide Hydrochloride
NDA number: NDA 21-855

Loperamide is a synthetic opioid μ-receptor agonist, and is classified into anti-motility agent category. At the therapeutic dose level, it does not pass the blood brain barrier. The main mechanism of its anti-diarrheal action is due to the reduction of intestinal motility. Loperamide at 4 mg PO daily decreases the stool frequency and liquidity, and controls fecal urgency. It alleviates symptoms of acute and chronic diarrhea.

Although it is indicated for treating chronic diarrhea associated with inflammatory bowel disease, treatment for longer than 10 days is not recommended (Imodium package insert, 2005). The most common side effects of loperamide are related to the impact on bowel motility (constipation, abdominal pain, distention, bloating, nausea, and vomiting). Additionally, drug interactions when loperamide is co-administered with the ART drugs ritonavir or saquinavir have been reported in the literature.

Limitations include tolerance and physical dependence. Tolerance occurs because prolonged use induces hepatic metabolism enzymes. Also, prolonged exposure triggers receptor desensitization to opioid agonists via receptor-mediated pinocytosis.

Risks of loperamide therapy include severe allergic reactions, constipation, decreased urination, swollen skin, and abdominal pain.

B) Lomotil
Trade name: Lomotil
Generic name: Diphenoxylate and Atropine
NDA number: 12-699

Lomotil is a combination of diphenoxylate (meperidine congener, opioid) and anti-cholinergic agent atropine. It inhibits intestinal motility. One of the contraindications in the Lomotil label is diarrhea associated with pseudomembranous enterocolitis or enterotoxin-producing bacteria. There have been rare reports of toxic megacolon; the label for Lomotil states that in some patients with acute ulcerative colitis, agents that inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon.

Limitations of diphenoxylate include tolerance and physical dependence also as for loperamide. Atropine, as an anti-cholinergic agent, may increase intracranial pressure, tachycardia, and bronchial asthma.

Risks of lomotil therapy include respiratory depression, convulsions, constipation, nausea, vomiting, tachycardia, bronchial asthma, hallucinations and coma.

2.3 Availability of Proposed Active Ingredient in the United States

"Dragon's Blood" is the dietary supplement version of Crofelemer in the United States. *Croton lechleri* is commonly known as *sangre de drago* in Peru and *sangre de grado* in Ecuador, both meaning dragon's blood. *Sangre de drago* latex has been available in the United States since before the passage of the Dietary Supplements Health and Education Act (DSHEA) in 1994, and it is listed on the old dietary ingredients list of plants submitted by the Utah Natural Products Alliance to the US Food and Drug Administration as part of the Administration's premarket notification program for New Dietary Ingredients.

According to the Applicant, to date Crefelemer has not been marketed outside the U.S.

2.4 Important Safety Issues with Consideration to Related Drugs

According to the clinical pharmacology studies, absorption of Crofelemer is minimal following oral administration. In the ADVENT study at the therapeutic dose (125 mg bid), less than 1% of plasma samples were above the detection limit.

Crofelemer treatment may delay the diagnosis and treatment of opportunistic infection diarrhea in HIV patients. The message that pathogen-specific diarrhea should be excluded prior to Crofelemer therapy has been adequately addressed in the labeling.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Crofelemer was studied under IND 51,818. A summary of the regulatory history of Crofelemer is listed as follows:

- The original IND (IND 51,818) was submitted by Shamen Pharmaceuticals, Inc. on November 1, 1996. (b) (4)

- IND 51,818 was then transferred to PS Pharmaceuticals, Inc. on April 23, 2002. The sponsor inactivated the IND from May 15, 2002 to April 2, 2004. PS Pharmaceuticals changed their name to Napo Pharmaceuticals, Inc., and changed the product's name to Crofelemer.

- On February 26, 2004, Napo Pharmaceuticals submitted an End-of-Phase 2 (EOP2) meeting request (b) (4) This meeting request was then transferred to the Division of Gastrointestinal and Coagulation

Drug Products (DGCDP) under IND 51,818 on March 29, 2004. The sponsor requested the IND be activated on April 2, 2004.

- The End of Phase 2 (EOP2) meeting was held on May 5, 2004. The outcome of the meeting was as follows:
  - (b) (4)
  - FDA agreed that the primary endpoint for a responder is 2 or less watery stools per week.
  - FDA agreed that pediatric studies may be deferred, provided that a pediatric study plan is submitted.
  - The sponsor agreed to conduct the 6-month oral gavage toxicity study in rats (b) (4)
  - The sponsor agreed to conduct 2-year carcinogenicity studies in mice and rats (b) (4). FDA agreed that these studies may be conducted as Phase 4 commitments.

- On October 20, 2006, Napo Pharmaceuticals submitted the protocol of a pivotal Phase 3 study (ADVENT Trial) for a Special Protocol Assessment (SPA). The Division responded with an advice letter dated December 4, 2006. The letter contained the following recommendations and requests:
  - Provide the reasons for pursuing a two-stage design.
  - Provide the rationale for the proposed statistical analysis plan.
  - If the protocol intends to treat highly active anti-retroviral therapy (HAART) associated diarrhea, it should exclude the patients currently not under HAART therapy.
  - For HIV diarrhea caused by opportunistic infections, anti-diarrhea therapy alone may delay the pathogen-specific therapy. To exclude these subjects, the stool test should be performed once a week for the 4-week assessment period. Patients who present with exacerbation of diarrhea should undergo repeat stool testing to rule out infectious etiologies. Any subject with a positive stool test should be withdrawn from the study.
  - The effect of Crofelemer on the absorption of anti-HIV drugs from the GI tract is unknown. Thus, patients should have HIV viral load (copies) evaluated prior to and immediately after the study. The pharmacokinetics of the anti-HIV drugs in the presence of Crofelemer therapy should be studied in patients with HIV rebound after the therapy.

- Negotiations regarding the SPA continued through October 2008 after the initiation of the trial. There was no final agreement letter sent to the Applicant.

- Crofelemer was transferred from Napo Pharmaceuticals, Inc. to Salix Pharmaceuticals, Inc. on December 9, 2009.

- The Pre-NDA meeting was held on January 19, 2011.
  - DGIEP advised the sponsor that the indication should reflect the specific patient population that was studied in the clinical trial based on the eligibility criteria.
  - The Division stated that the lack of 1 year exposure is unacceptable for a chronic therapy; the sponsor proposed submitting the long-term safety data later during the NDA review cycle.
  - (b) (4)
  - The Division stated that it does not appear that a finalized agreement on the SPA was achieved.
  - The deferral of pediatric studies is subject to review of the pediatric plan which should be submitted with the NDA.

- The CMC pre-NDA meeting was held on May 24, 2011 to review the sponsor's responses to the Agency's CMC questions posed at the pre-NDA meeting on January 19, 2011.

- On December 6, 2011, the applicant submitted the original NDA for the indication of control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.

2.6 Other Relevant Background Information

Diarrhea occurs in about 50% of HIV-infected patients in their disease courses in North America (Lew, 1997; Stephanie, 2000; Know, 2000; Tinmouth, 2007; Smith, 1992; Colebunders, 1987; Mayer, 1994). The majority (50 to 80% of the diarrhea) are caused by opportunistic infections (Simon, 1993; Carcamo, 2005). In the era of Highly Active Antiretroviral Therapy (HAART), the incidence of opportunistic infection diarrhea has decreased and ART associated diarrhea has increased (Kartalija, 1999). In principle, pathogen-specific therapy is used as first line treatment of opportunistic infection diarrhea.

Etiologies of HIV associated diarrhea
A) Opportunistic infection:

Bacteria: *Shigella, Salmonella,* and *Campylobacter* species with fluoroquinolones. A *Clostridium difficile*-toxin assay should always be part of a work-up. Treat *C. diff* positive patients with metronidazole, 250 mg PO tid for 7 to 10 days (Kartaja, 1999).

Parasites: *Cryptosporidium parvum*: Pathogen-specific therapy for cryptosporidiosis was disappointing. However, in HIV-infected patients with CD4 cell counts of > 180/mm^3, the diarrhea resolved spontaneously in 7 to 28 days, whereas the diarrhea persisted in 87% of those with CD4 cell counts of < 180/mm^3 (Flanigan, 1992). Thus, HAART is protective against this diarrhea (Manabe, 1998)

Mycobacteria: *Mycobacterium avium* complex (MAC): Suppressive therapy with macrolide and ethambutol should be discontinued, when CD4 cell counts are > 250/mm^3 under HAART (Kartalija, 1999).

Viruses: Cytomegalovirus (CMV): up to 20% of diarrhea in AIDS patients; Treating with ganciclovir and foscarnet. Suppressive therapy with HAART is critical. When CD4 cell counts > 250/mm^3 with HAART, ganciclovir and foscarnet should be discontinued (Macdonald, 1998; Tural, 1998).

B) HIV enteropathy diarrhea:
In 15% to 46% of HIV-infected patients with diarrhea, no pathogen can be identified; therefore, this is referred to as HIV enteropathy (Bellosillo, 1998). Opening of the tight junctions between intestinal epithelial cells by HIV-stimulated cytokine release (TNF or IFN-γ) suggests a direct mechanism of diarrhea; i.e., HIV infection induced cell-mediated immune cytotoxicity. It damages intestinal epithelium and junctional complexes, and causes apoptosis of uninfected cells, leading to exudative enterocolitis and diarrhea (Kotler, 2005; Smith, 1992; Ullrich, 1992). Anti-retroviral therapy improves this type of diarrhea.

C) Diarrhea as a Side Effect of HAART:
Up to 40% of HIV infected patients receiving combinations of antiretroviral agents experienced moderate-to-severe diarrhea, significantly complicating treatment (Kartalija, 1999). Over 28% of ART discontinuations were due to GI intolerance (mainly due to diarrhea) (Elzi, 2010).

Experimental studies in mice suggest that protease inhibitors (nelfinavir, indinavir) and nucleoside reverse trascriptase inhibitor AZT significantly increase secretions of chloride and net water (Braga, 2010). There is no effective anti-diarrhea therapy for this type of diarrhea.

D) Diarrhea caused by Kaposi's sarcoma (KS) and lymphomas:
KS is a common consequence of HIV infection (especially in homosexual men) and is associated with human herpes virus 8 infection. KS lesions involve skin, lymph nodes, and intestinal tract with a wide dissemination trend. About one third of the

patients with Kaposi's sarcoma subsequently develop a second malignancy, such as lymphoma. There is no treatment for KS diarrhea.

Mechanisms of chronic diarrhea

A) Secretory diarrhea:

Increased intestinal ion secretion

- Viral damage to mucosal epithelium
- Bacterial enterotoxin mediated
- Neoplastic
- Drug induced

B) Exudative diarrhea:

Involving cell-mediated immune cytotoxicity: Mucosal cell death, inflammatory cytokine release, leading to purulent, bloody stools.

- HIV infection induced enterocolitis

D) Osmotic diarrhea:

- Excessive osmotic forces from luminal solutes leading to stool > 500 mL/day

E) Malabsorption diarrhea:

- Improper absorption with increased osmolarity

F) Motility disorders:

- Intestinal neuromuscular dysfunction

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission appeared to be acceptable. The study report and datasets were substantially complete and allowed an independent review.

3.2 Compliance with Good Clinical Practices

According to the Applicant, Study ADVENT was conducted based on Good Clinical Practice (GCP) guidelines, as documented in the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA).

DSI Audits for Study ADVENT

(1) Selection of Inspection Sites

There are a total of 70 study sites in the United States. Division of Scientific Investigations (DSI) conducted an audit of three selected sites (Sites #60, #45 and #11). Selection of the inspection sites was based on (1) Study site that had ≥40% of patients who achieved the clinical response during the PC Phases (the average achievement of ADVENT was 18%); and (2) Study sites that had more patients in the 125 mg Crofelemer treatment group and placebo than the others:

- Site #60: 4 patients in Crofelemer 125 mg group of PC Phase; 75% (3/4) patients achieved the clinical response, compared to the 0% (0/4) of placebo.

- Site #45: 4 patients in Crofelemer 125 mg group of PC Phase; 75% (3/4) patients achieved the clinical response, compared to the 0% (0/3) of placebo.

- Site #11: 5 patients in Crofelemer 125 mg group of PC Phase; 40% (2/5) patients achieved the clinical response, compared to the 25% (1/4) of placebo.

(2) Results

Site #60:

a. What was inspected: The field investigator reviewed the records of all 9 subjects who completed the study including consent forms, drug accountability records, CRFs and patient diaries.

b. General Observations/Commentary:
The inspection revealed few protocol violations: Subject # 016007 did not have the screening ECG until Visit 1 and was not reviewed until the day after dosing; protocol- specified physical examination of the rectum, lymph nodes, genitourinary system/gynecological organs were not made for any subject; failure to question 4 subjects at 1-2 visits about adverse reactions and concomitant medications.

Also there were inaccurate records in that a copy of the original IVRS diary entries was not available at the site, but only the sponsor provided printouts. When another field investigator inspected the sponsor (Salix), the original entries from the patients were found and were similar to the print-outs.

c. Assessment of data integrity:
These violations will not affect the validity of the data and the data obtained at this site can be used in support of the NDA.

Site #45:

a. What was inspected: The field investigator reviewed all the records of the 7 subjects who completed the study. This included consent forms, drug accountability records, CRFs and patient diaries.

b. General Observations/Commentary: The inspection revealed: inadequate consent forms in that 4 enrolled subjects were not re-consented with the new version; a protocol violation in that subject # 017 was enrolled before a protocol required urine test for opiates; The site had printouts, but not the original IVRS diary responses of the subjects. These originals were found during the sponsor inspection.

c. Assessment of data integrity: These violations would not affect the validity of the data. The data from this site can be used in support of the NDA.

Site #11:

a. What was Inspected: At this site, 12 subjects were randomized and 6 subjects completed the study. The field investigator reviewed all the records of the study at this site

b. General Observation/Commentary: The inspection revealed 2 violations: record un-availability and inaccurate records, in that a copy of the original entries of the patients' diaries in the IVRS was not available at the site; Also, there were discrepancies between the subjects' charts and the eCRFs. These differences were minor evaluations of the AEs.

Sponsor/Monitor/CRO:

Salix Pharmaceuticals, 8510 Colonnade Center Dr., Raleigh, NC 27615

a. What was inspected: The field investigator audited Protocol NP303-101 (ADVENT trial) at the Sponsor's site and focused on the following 4 clinical sites: M. Wholfeiler, site 60; M. Somero, site 45, P. Clay, site 11, (b) (6) The first 3 sites were requested for inspection by the Division (b) (6) The field investigator reviewed general correspondence and study master files: site monitoring, handling of adverse events, information and procedures related to the "interactive voice response system (IVRS), subject diaries and the files of subjects at the sites. The inspection reviewed also IRB documents, CRFs, data collection and study drug accountability.

b. General observations/commentary: The field investigator reported that a copy of the original entries of the IVRS were found similar to the printouts which were in the 3 sites inspected. The sponsor was requested in the future, to provide the sites with a copy of the original data entries, not only the printouts.

One violation was observed during the review, that the sponsor failed to "select only investigators qualified by training and experience as appropriate experts to investigate the drug" 21 CFR 312.53(a)

Dr. Patrick Clay is a Pharm D. and there was no sub-investigator who is an M.D. to supervise the medical aspects of the study

d. Assessment of data integrity:
The inspection revealed that the data generated from the 3 sites inspected can be used in support of the NDA.

Overall Assessment and Recommendations by Division of Good Clinical Practice Compliance, OSI

Drs. Khairy Malek and Susan Leibenhaut commented: Inspection of the 3 sites: Drs Wholfeiler, Somero and Clay as well as the sponsor, Salix Pharmaceuticals showed acceptable results. The violations mentioned above at each site would not affect the validity of the data.
The data from these sites can be used in support of the NDA.

DGIEP MO Comments: Agree with Drs. Khairy Malek and Susan Leibenhaut.

3.3 Financial Disclosures

The Applicant has submitted FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

Medical Officer Comment:
The Applicant has adequately disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not bring up concerns which would possibly jeopardize the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing, and Controls (CMC) review was performed by the Product Quality Reviewer Nina Ni, Ph.D. Dr. Ni stated that "from the Office of New Drug Quality Assessment (ONDQA) perspective, this NDA is ***not*** recommended for approval" (DARRTS on July 13, 2012). ONDQA has recommended a Complete Response for NDA 202-292, because the applicant has ***not*** provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. While numerous

outstanding quality related issues remain unresolved, the primary ONDQA concern is the lack of a reproducible and robust test for the Identity of the drug substance. The lack of this test prevents ONDQA from determining if the proposed commercial product is comparable to the product used in clinical trials. It also prevents the assurance of comparability among commercial lots of drug product, and also is not capable of detecting intentional or unintentional adulteration of the drug substance (ONDQA Assessment for Center Director Briefing on August 6, 2012).

Medical Officer Comments:
The clinical reviewer believes that the identity of Crofelemer has been demonstrated, i.e., proanthocyanidin oligomers (Ubillas, 1994). It is the distribution of the oligomers that is not entirely clear.

The Applicant has conducted numerous studies in an attempt to explore the distribution. For example, the Applicant has studied 222 historical batches of Crofelemer using reverse phase HPLC-UV to establish the specification comparing with a standard drug substance batch, and 101 batches using mass spectrometry to estimate the average molecular weight. Although the specification of (b) (4) was accepted in her review, Dr. Ni concluded that the structural data do not concretely define the identity of Crofelemer (DARRTS, July 13, 2012).

From the clinical reviewer's view point, further characterization of the oligomer distribution is not critically important at the present time, because the chemical identity of Crofelemer is known, and that to "concretely" define the distribution of the oligomer may delay the approval of Crofelemer for the treatment of HIV diarrhea.

4.2 Clinical Microbiology

Crofelemer is a botanical product. There is no clinical microbiological issue raised by the current submission.

4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology review was performed by Sruthi King, Ph.D. She did not identify any issue that would preclude approval.

The highest Crofelemer dose in rat studies, 600 mg/kg, is equivalent to a human dose of 97 mg/kg (5800 mg for a 60-kg human), or 46 times the therapeutic dose of 125 mg. In dogs, 600 mg/kg is equivalent to 333 mg/kg in humans (19980 mg for a 60-kg human), or 160 times the therapeutic dose of 125 mg.

The cardiovascular effects of Crofelemer were evaluated in conscious freely moving beagle dogs. Following oral doses of 200 mg/kg and 600 mg/kg of Crofelemer, clinical observations included red, black, or brown feces; soft, watery, and/or mucoid feces; and/or black or brown material below the cage (fecal material). No effects of Crofelemer on electrocardiogram parameters or mortality were observed. The no-observed-adverse-effect level (NOAEL) was estimated to be 600 mg/kg in dogs (a human equivalent dose 160 times the therapeutic dose).

The potential effects of Crofelemer on pulmonary function were evaluated in rats. With respect to the basic respiratory endpoints evaluated in this study, oral administration of Crofelemer produced no adverse effects at doses up to 600 mg/kg, which is equivalent to a human dose 46 times the therapeutic dose. No effects on mortality were observed over the course of the study. The following test-article-related clinical findings were considered adverse effects in this study: brown material around the mouth, yellow or brown discolored hair in the abdominal region, and/or difficult breathing in 1 of 8 animals in each of the 200 and 600 mg/kg dose groups. Therefore, the NOAEL for clinical observations was 60 mg/kg in rats (equivalent to a human dose 4.6 times the therapeutic dose).

4.4 Clinical Pharmacology

The Clinical Pharmacology review was performed by Kristina Estes, Pharm.D. Dr. Estes did not identify an issue that would preclude approval.

4.4.1 Mechanism of Action

Crofelermer inhibited the cystic fibrosis transmembrane regulatory (CFTR) Cl^- channel with maximum inhibition of about 60% and IC_{50} about 7 µM (Tradtrantip, 2010). Crofelemer action also stabilizes the channel closed state several hours after washout. Because of its large molecular size and polarity, it was membrane-impermeable, and the action was located at an extracellular site on CFTR. Crofelemer was also found to inhibit the intestinal calcium-activated Cl^- channel (CaCC) by a voltage-independent inhibition mechanism with maximum inhibition >90% and IC_{50} about 6.5 µM. The dual inhibitory action of Crofelemer on two structurally unrelated prosecretory intestinal Cl^- channels may account for its intestinal anti-secretory activity (Tradtrantip, 2010; Crutchley, 2010).

Studies by Braga in mice suggested that antiretroviaral drugs such as protease inhibitors (e.g., nelfinavir, indinavir) and nucleoside reverse trascriptase inhibitor (e.g., AZT) significantly increase net water secretion and electrolyte (Cl^-) secretion (Braga, 2010). To study the effect of Crofelemer on anti-retroviral therapy (ART) induced

diarrhea, 98% of the ITT patients had concomitant ART (one or more anti-retroviral medications). The diarrhea lasted at least one month prior to the randomization.

4.4.2 Pharmacodynamics

Crofelemer acts locally in the GI tract. At the therapeutic dose level, its systemic absorption is minimal. Thus, pharmacodynamic studies are not applicable.

4.4.3 Pharmacokinetics

The pharmacokinetic findings for Crofelemer are summarized as follows:

- The absorption of Crofelemer (enteric-coated tablets or beads) was minimal following oral dosing in healthy adults or in human immunodeficiency virus-positive (HIV+) subjects, in either the fasted or fed state. Across all the PK studies, less than 5% of healthy and HIV-associated diarrhea subjects had detectable plasma concentrations of Crofelemer following oral dosing. Crofelemer was detected in plasma samples in 3 of the 6 trials; however, the plasma Crofelemer concentrations were low, sporadic, discontinuous, and not sufficient for calculation of pharmacokinetic parameters. The high degree of human plasma protein binding (approximately 97%) further limits systemic exposure to Crofelemer. At the therapeutic Crofelemer dose of 125 mg twice daily in ADVENT, less than 1% of plasma samples had Crofelemer concentrations above the limit of quantification (LOQ).

    - The clinical pharmacokinetics data indicating minimal systemic absorption are consistent with *in vitro* membrane permeability studies in Caco-2 cells, which demonstrate that ^{14}C-methylated Crofelemer is not translocated to a measurable extent across cell monolayer. *In vivo* studies in animals also suggest that Crofelemer has a very low oral bioavailability.

    - *In vitro* data indicate, at clinical concentrations, no cytochrome P450 (CYP)-mediated metabolism or gastrointestinal (GI) absorption-based interactions with other drugs.

- Consistent with *in vitro* results on drug-drug interactions, concomitant use of Crofelemer and antiretroviral agents nelfinavir, zidovudine, and lamivudine in healthy adults resulted in no effect on nelfinavir and zidovudine systemic exposure and a small decrease in lamivudine systemic exposure. The minimal pharmacokinetic changes for lamivudine are not expected to cause medically relevant changes in the pharmacodynamic effects of antiretroviral therapy (ART).

- Analyses of population pharmacokinetic data for antiretroviral compounds from Stage 1 of ADVENT (HIV+ subjects) showed no significant pharmacokinetic interaction between Crofelemer and the antiretroviral compounds at any Crofelemer dose. These data from HIV+ subjects and results of Study 37554-103 (healthy subjects), which demonstrated minimal effects of Crofelemer coadministration on ART pharmacokinetics, are consistent with the absence of significant effects of Crofelemer on parameters reflecting HIV status, and with the essentially undetectable plasma exposure to Crofelemer at the doses studied in ADVENT. The profile of increases or decreases from baseline in key HIV parameters (HIV viral load, CD4, and CD8 counts) did not suggest any medically relevant trends during Crofelemer treatment in the ADVENT trial. There was no indication that Crofelemer had an adverse impact on the pharmacodynamic effects of ART.

- The cardiac safety of Crofelemer was assessed in nonclinical studies (hERG K+ inhibition and dog cardiovascular safety pharmacology).

    - In the human hERG inhibition study, the 50% inhibitory concentration (IC_{50}) for the hERG potassium ion (K+) channel was > 135-fold above the highest unbound plasma concentration observed in a human pharmacokinetics study and 1392-fold above the highest unbound plasma concentration observed in ADVENT. The > 135-fold margin between the hERG IC_{50} and the highest unbound plasma concentration of Crofelemer is substantially greater than the 30-fold margin considered to be safe regarding the potential risk of corrected QT (QTc) interval prolongation for drugs in clinical development (Redfern, 2003).

    - In dogs receiving Crofelemer at doses up to 600 mg/kg (160 times the therapeutic human equivalent dose of 125 mg), no cardiovascular effects were observed (CRSP0300). Specifically, there were no systematic or substantial changes noted in ECG data, including the QT and QTc intervals, over the course of the study.

- In clinical studies, results show no evidence of Crofelemer dose-response for QT/QTc prolongation at therapeutic (125 mg bid) or supratherapeutic (500 mg bid) doses, and show no effects on QTc prolongation. The upper bound of the 95% one-sided confidence intervals (CIs) for the placebo-corrected change in QTc interval (corrected using Fridericia's formula, QTcF) did not exceed the regulatory threshold of 10 msec at all time points. A draft protocol for a thorough QT study in healthy adults was submitted to IND 51818 on November 7, 2011 (S-110) for review by the FDA QT-IRT committee. Recommendations from the QT-IRT committee were sent to the Sponsor in January 2012. The study was completed and the study report was recently submitted. The QT-IRT committee has been consulted to review this study report.

- Crofelemer is a substrate for one of the CYP isoenzymes *in vitro*. One Crofelemer metabolite, 4'-O-methyl epigallocatechin (4-MEGC), and several minor metabolites were detected in urine from an *in vivo* study in Sprague-Dawley rats. Also, Crofelemer and Crofelemer metabolites were identified in urine samples from human subjects who received 2000 mg/day of Crofelemer (powder dissolved in 0.2% xanthan gum) for 7 days in study SP-303-I-04. No Crofelemer metabolites have been identified in other human studies.

4.5 Botanical Review Team

The botanical products review was performed by Drs. Jinhui Dou and Shaw Chen. Drs. Dou and Chen did not identify an issue that would preclude approval.

The Botanical Review Team has the following recommendations on Post-Approval Botanical Issues:

- The applicant should take concerted effort to prevent the over harvesting of botanical raw material (BRM) from the wild grown trees in the current eco-geographic regions (EGRs).
    - The applicant should continue to evaluate the applicability of BRM collected from other EGRs, and further analyze the chemical profiles of BRM. Other means to qualify additional EGRs, such as post-approval bridging clinical studies (even with other related but not the same indication) or developing and using a medically relevant bioassay should be evaluated.
- The applicant should continue to reinforce the implementation of the established Good Agricultural and Collection Practice (GACP) on Crude Plant Latex (CPL) quality control, storage, and transportation, to prevent misuse and/or accidental contamination.
- Continue the characterization of the BRM and botanical drug substance (BDS) as new separation and detection technologies become available.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary efficacy database contains one new clinical study (Study NP303-101 or ADVENT trial) performed in two Stages:

1. Stage 1: Crofelemer 125 mg, 250 mg, and 500 mg tablets orally twice daily for four weeks during the placebo-controlled period; and for 20 weeks during the placebo-free period;

2. Stage 2: Crofelemer 125 mg twice daily for 4 weeks during the placebo-controlled period; and for 20 weeks during the placebo-free period;

Primary endpoint: Clinical response, defined as ≤ 2 watery bowel movements per week for at least 2 of 4 weeks during the 4-week period.

In addition, two supportive clinical studies (37554-210 and 37554-209) were also submitted using change from baseline in daily stool weight during the treatment as the primary endpoint (Table 1).

The safety database consists of the three placebo-controlled trials: Studies ADVENT, 37554-210, and 37554-209 in HIV patients. A total of 696 patients were evaluated; 229 HIV positive patients received daily doses of 250 mg (125 mg bid) and 467 HIV positive patients received daily doses ≥ 250 mg. The duration was ≤ 1 month for 2 of these trials (Studies 37554-209 and 37554-210), and up to 6 months for Study ADVENT.

Table 1: Overview of Individual Study reviewed

Study	Design	Patient Population
ADVENT	Randomized, two stage design; 4-week placebo-controlled periods, followed by 20-week placebo-free periods. Stage 1: dose selection (125 mg, 250 mg, and 500 mg PO, bid); Stage 2: dose assessment (125 mg PO, bid). Participation in both stages not allowed. Primary endpoint: Proportion of patients who had clinical response, defined as ≤ 2 watery bowel movements per week for at least 2 of 4 weeks.	Adult HIV positive patients N = 236; 233 (98%) pts on ART
37554-209	Randomized, placebo-controlled, double-blind; 500 mg qid for 4 days Primary endpoint: Change from baseline in daily stool weight during the treatment	Adult HIV positive patients N=43; 37 pts (86%) on ART
37554-210	Randomized, placebo-controlled, double-blind; 250 mg tablets; 500 mg tablets, or 500 mg beads PO qid for 4 days. Primary endpoint: Change from baseline in daily stool weight during the treatment	Adult HIV positive patients, N=302; 291 pts (96%) on ART

From the Clinical Study Reports.

5.2 Review Strategy

Efficacy assessment was based on one Phase 3 clinical study (Study ADVENT), and two supportive studies, Study 37554-210 (Phase 3) and Study 37554-209 (Phase 2). The supportive studies used a different primary endpoint, daily stool weight. The supportive studies also used a different formulation than that used in Study ADVENT.

Safety assessment was based on three clinical studies (Studies ADVENT, 37554-209, and 37554-210) in HIV patients. The studies were conducted by Salix, Shaman, and Napo Pharmaceuticals. All of the results in the submission were reviewed. The data supported a substantive clinical review. Literature was not relied upon to support the safety and efficacy.

The review methods are summarized as follows:

1) Literature search to understand that HIV diarrhea is a complex illness, and that multiple etiologies and mechanisms of HIV diarrhea may influence the efficacy outcomes of Crofelemer treatment.

    - Effects of CD4 cell counts on spontaneous recovery of HIV diarrhea:
        - When CD4 counts > 200, opportunistic infection diarrhea is often self limited.

    - Effects of concomitant ART on spontaneous recovery of diarrhea:
        - In the presence of ART, opportunistic infection diarrhea and HIV infection associated enteropathy diarrhea may be self limited.

    - Effects of different HIV diarrhea etiologies on spontaneous recovery of diarrhea
        - Opportunistic infection diarrhea and HIV enteropathy diarrhea may be subject to spontaneous recovery, in the presence of ART and CD4 counts > 200.

        - Protease inhibitor induced diarrhea may not be subject to spontaneous recovery, despite the use of ART and CD4 counts > 200.

2) Literature search to investigate the unmet medical needs in the field of HIV diarrhea.
    - Identify the needs of HIV patients who have persistent diarrhea, despite the use of loperamide and/or lomotil.

    - Identify the reasons why HIV patients discontinue ART:
        - Gastrointestinal adverse reactions (diarrhea and vomiting) are the leading cause of ART discontinuation.

- Identify the evidence that treating diarrhea is able to improve adherence to ART containing protease-inhibitors.

3) Exploratory subgroup analyses of the clinical trial data in ADM users and protease inhibitor users.

A comprehensive safety review of the above three studies was performed based on treatment-emergent adverse events, vital signs, ECG and laboratory tests.

5.3 Discussion of Pivotal Study ADVENT

To avoid duplication, this section is focused on discussion of the efficacy results of Study ADVENT.

Studies 37554-209 and 37554-210 used a different formulation and had a different primary efficacy endpoint (Change of daily stool weight from baseline) that was not used for the labeling; and are briefly summarized in Section 9.2 Appendices 2 and 3. The results of these two studies were consistent with and supportive to the ADVENT.

5.3.1 Indication

The proposed indication is: “for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.”

5.3.1.1 Methods

Determination of efficacy is based on the primary efficacy endpoint: the proportion of patients in the Intent-to-Treat (ITT) population who experienced clinical response (defined as ≤ 2 watery bowel movement per week for at least 2 of 4 weeks during the 4-week efficacy assessment period).

Secondary efficacy endpoints during the 4-week efficacy assessment period were as follows:

- Number of watery bowel movements per day;
- Daily stool consistency score;
- Daily abdominal pain or discomfort score;
- Number of days per week that subjects experienced urgency;
- Number of days per week that subjects experienced fecal incontinence; and
- Number of bowel movements per day; and

- Proportion of subjects undergoing an unscheduled visit for a significant worsening or clinically significant exacerbation of diarrhea.

Safety variables included treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious adverse events (SAEs), TEAEs resulting in study drug discontinuations, clinical laboratory parameters, vital signs, electrocardiogram (ECG) findings, diarrhea exacerbation, and HIV-1 viral load, and CD4 cell counts.

5.3.1.2 General Discussion of Endpoints

Appropriateness of Primary Endpoint Measurements
The primary efficacy endpoint was clinical response, defined as 2 or less watery bowel movements per week, during at least 2 of the 4 weeks of the PC phase. The frequency of watery bowel movements was selected based on the results of the previous octreotide clinical trial of refractory HIV diarrhea (Simon, 1995) and from the Studies of 37554-209 and 37554-210 of Crofelemer (Section 9.2, Appendices 2 and 3).

Because patients were required to report at least 5 days of watery bowel movements during the last 7 days of the Screening phase to be randomized into the study, the primary endpoint (≤ 2 watery bowel movements per week) represented an improvement of diarrhea for at least 50% of the time in HIV patients as compared with baseline. Because patients with HIV infection and chronic diarrhea are seriously ill, and most participating patients had previously tried ADM with inadequate efficacy, a 50% reduction of diarrhea time would represent a clinical benefit in the treatment of this serious and debilitating condition.

DGIEP reviewed and agreed with this endpoint during an End of Phase 2 meeting on May 5, 2004 (see the meeting minutes on June 1, 2004 in DARRTS).

The weekly based responder, instead of daily based responder, reflected the inherent variability of diarrhea and the expectations for clinical improvement in response to anti-diarrhea therapy in the HIV population. Prior evaluation of stool output with Crofelemer treatment in Studies 37,554-209 and 37,554-210, including stool frequency and stool weight, demonstrated those measures to be highly variable on a daily basis. Therefore, assessments over 1-week intervals were chosen for the primary efficacy endpoint in this Phase 3 trial.

5.3.1.3 Design of Study ADVENT

This study was a randomized, double-blind, parallel-group, placebo-controlled, multi-center, two-stage trial. It was performed using an adaptive trial design comprised of a dose-selection stage (Stage 1) and a dose assessment stage (Stage 2). Both stages

consisted of a 10 (± 4) day, single-blind, placebo screening phase; a randomization and a 31-day, double-blind, placebo-controlled (PC) treatment phase; and a subsequent 20-week, placebo-free (PF) extension phase. All study procedures performed in Stage 1 and Stage 2 of the trial were identical. Subjects participated in either Stage 1 or Stage 2 of the study (i.e., subjects were not allowed to participate in both study stages).

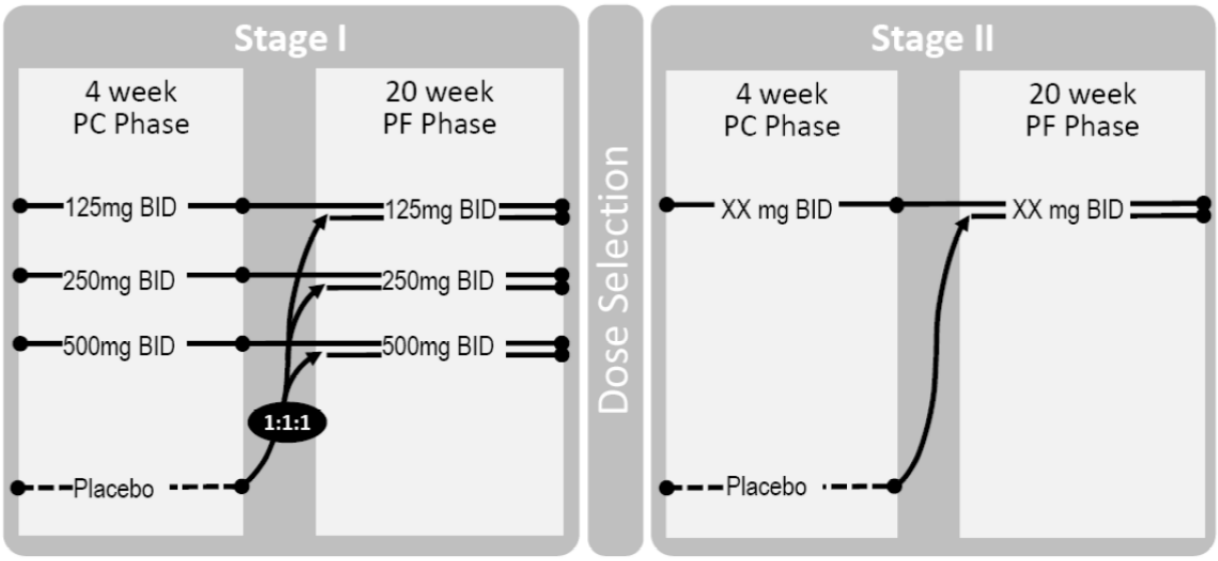
Stage 1:
In Stage 1 (dose-selection stage), the double-blind phase had 4 arms: 3 doses of Crofelemer (125 mg bid, 250 mg bid, and 500 mg bid) and placebo bid. Subjects were randomized in a 1:1:1:1 ratio to the 4 treatment groups. Subjects on Crofelemer who entered the 20-week PF extension phase remained on their same dose, and subjects on placebo were re-randomized to 1 of the 3 Crofelemer doses. After approximately 200 subjects (i.e., about 50 subjects per arm) completed the PC treatment phase of Stage 1, an interim analysis was conducted and the dose of Crofelemer that appeared to show better efficacy and safety data was selected by an Independent Analysis Committee (IAC) for comparison to placebo in Stage 2. The duration of the interim analysis period was kept to less than or equal to 8 weeks.

Stage 2:
Stage 2 had 2 arms in the double-blind, PC treatment phase: the dose of Crofelemer selected based on Stage 1 and placebo. Subjects were randomized in a 1:1 ratio. All subjects who entered the 20-week PF extension phase in Stage 2 received the previously selected optimal dose of Crofelemer. Enrollment was completed when approximately 150 subjects were randomized in Stage 2. Efficacy assessments in the study were based on subject diaries, which were entered daily into the Interactive Voice Response System (IVRS). The subject diaries captured diarrhea symptoms (stool consistency, stool frequency, sense of urgency, fecal incontinence, and abdominal pain or discomfort), adherence to study medication and ART, and use of ADM or prohibited medications. The information collected from these diaries was used to assess treatment outcomes for the trial. The study diary Interactive Voice Response System (IVRS) and IVRS definitions are described in Section 9.2, Appendix 1.

During both Stage 1 and Stage 2, patients first entered a single-blind placebo screening phase lasting 10 (±4) days, during which stool frequency, consistency, and urgency symptoms were entered into the patient diaries. Patients who reported in their diary at least 1 or more watery bowel movements per day on at least 5 of the last 7 days of the Screening phase, and urgency on at least 1 of the last 7 days were eligible for randomization.

Figure 1 provides an overview of the stages and illustrates how subjects were grouped for primary and secondary efficacy analyses.

Figure 1: Stages of the ADVENT Study and Design of Efficacy Analyses

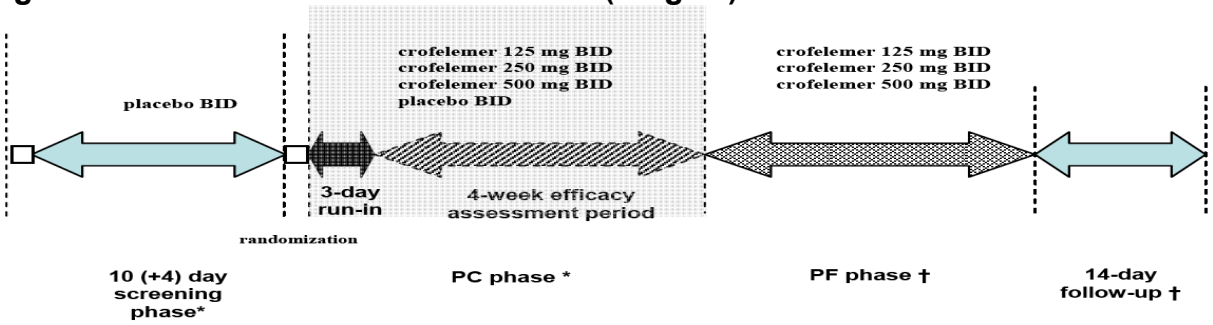


Abbreviation: PC = placebo-controlled; PF = placebo-free; and BID = twice daily.

Stage 1: Dose Selection Stage

In Stage 1 (dose-selection stage), the double-blind phase had 4 arms: 3 doses of Crofelemer (125 mg bid, 250 mg bid, and 500 mg bid) and placebo bid. Crofelemer or placebo was randomized 3:1 (1:1:1:1 randomization ratio). Approximately 200 patients (~50 patients per arm) were enrolled. An overview of the treatment phases for Stage 1 is provided in Figure 2.

Figure 2: Overview of Treatment Phases (Stage 1)



* ADM prohibited
† ADM permitted *ad libitum*
Abbreviation: ADM = antidiarrheal medication; PC = placebo-controlled, and PF = placebo-free

See Section 9.2, Appendix 1 for the Schedule of Study Assessments.

Eligible patients who enrolled in Stage 1 signed informed consent and entered a 10 (±4)-day Screening Phase (see Figure 3). The Screening phase started with a

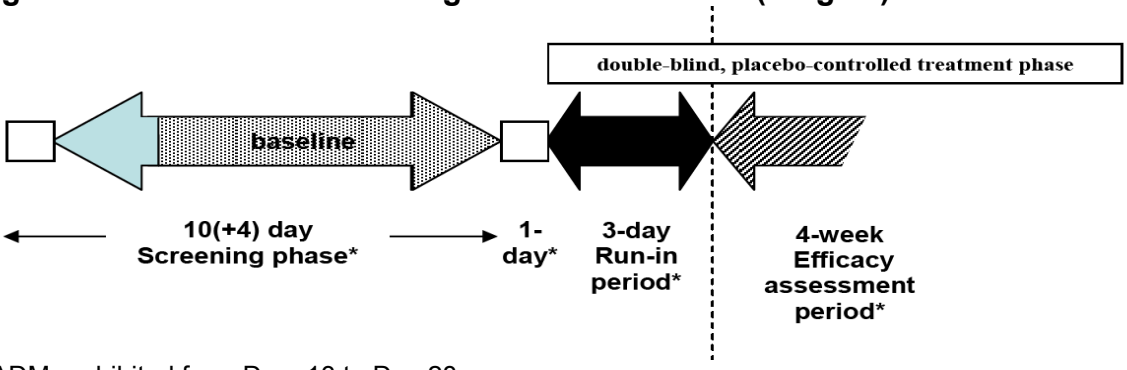
Screening Visit (the first open-square, Visit 0) that included a detailed medical history and physical, including history of HIV-related disease and co-morbidity, physical examination, stool examinations, electrocardiography (ECG), and laboratory analysis (including a CD4 count and serum pregnancy test).

Study medication (placebo) and IVRS entries started for all patients on the day following the Screening Visit and all use of ADMs was discontinued. Further use of ADMs was prohibited throughout the Screening phase, Randomization visit, and PC phase. Study medication in the Screening phase consisted of single-blind placebo bid until the morning of randomization (Visit 1, the second open square). Only patients were blinded to the use of placebo during screening.

The IVRS data obtained during the last 7 days of the single-blind screening phase served as baseline for all statistical evaluations. Patients with less than 5 days of efficacy data (via IVRS) were not randomized. Eligibility for the double-blind, PC phase was determined by review of IVRS entries and other screening criteria at the Randomization visit (Visit 1, the second open square). Patients who met all IVRS and screening criteria entered the double-blind, PC treatment phase.

The PC phase consisted of an initial 3-day run-in period followed by a 4-week efficacy assessment period. The 3-day run-in period was based on past observations with Crofelemer and was designed to ensure that the effects of study medication were fully established prior to the collection of data for efficacy assessments. Data captured on the IVRS during this 4-week efficacy assessment period served as the basis for assessment of the primary endpoint.

Figure 3: Overview of Screening and Run-In Period (Stage 1)



* ADM prohibited from Day -13 to Day 28

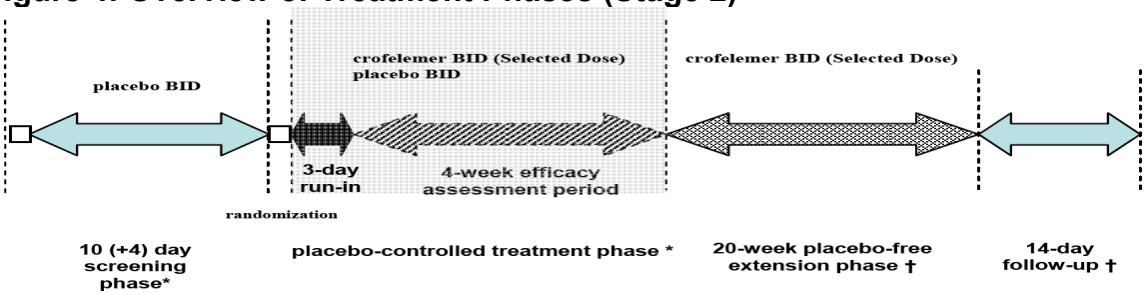
Patients who completed the PC phase entered a 20-week PF extension phase. Patients in the Crofelemer 125 mg bid, 250 mg bid, or 500 mg bid groups continued to receive those therapies throughout the PF phase; patients who received placebo were re-randomized to 1 of the 3 Crofelemer treatment regimens. Use of ADM was permitted during the extension phase. All subjects (Stage 1 or Stage 2) who completed the study or who discontinued early were followed for 14 days after stopping study medication.

Stage 2: Dose-Assessment Stage

Stage 2 consisted of 2 treatment arms in the double-blind, PC phase: the optimal dose of Crofelemer selected from Stage 1 and placebo. The chance of receiving Crofelemer or placebo was 1:1. Approximately 150 subjects were planned for inclusion in Stage 2. Enrollment was stopped when approximately 125 subjects were randomized, between Stages 1 and 2, to both the optimal Crofelemer dose group and to the placebo group, respectively.

An overview of the treatment phases for Stage 2 is provided below in Figure 4. The design of the treatment phase was identical for Stage 2 (Figure 4) and Stage 1 (Figure 2). All study procedures performed in Stage 2, including the subject IVRS diaries were identical to Stage 1. All subjects who entered the 20-week, PF phase in Stage 2 received the optimal dose of Crofelemer.

Figure 4: Overview of Treatment Phases (Stage 2)



* ADM prohibited
† ADM permitted *ad libitum*

5.3.1.4 Eligibility/Inclusion and Exclusion Criteria

Selection of Study Population

The study population consisted of patients with a confirmed diagnosis of HIV along with a history of diarrhea of at least 1 month duration. Participating patients had no identifiable non-HIV infectious or neoplastic etiology for their diarrhea, and individuals with CD4 cell count < 100/mm^3 were excluded due to the high risk of opportunistic infections. Patients were on a stable ART regimen and other therapies for associated conditions including prophylactic antibiotics for pneumocystis pneumonia (PCP) or infection for 4 weeks prior to Screening and were able to remain on this stable regimen during the Screening and Baseline phases and throughout the PC phase. This restriction was designed to avoid the confounding effects of a change in ART on stool frequency and consistency. To ensure the homogeneity of the study population, only patients using stable ART were permitted to enter the trial.

Patients who relied on intermittent, as-needed use of opioid pain medications were excluded from this study. Opioid pain medication is frequently used in the HIV-positive population for the treatment of neuropathies and HIV-associated conditions. However, opioids have a recognized effect on bowel movement frequency and consistency which had the potential to confound efficacy assessments. Therefore, only patients on methadone, buprenorphine, or buprenorphine/naloxone therapy for the purpose of pain management or addiction management that was stable for 3 months and fentanyl patch therapy that was stable for 4 weeks were allowed to enter the study.

The full inclusion criteria, exclusion criteria, and withdrawal criteria are provided in Section 9.2, Appendix 1.

5.3.1.5 Prior and Concomitant Medications

All medications taken for the 4 weeks prior to study entry were recorded on the concomitant medications CRF page, with the exception of the following medications that required a record of use for 3 months prior to study entry: methadone, buprenorphine, or buprenorphine/naloxone therapy. Concomitant medications taken throughout the study, and changes to existing concomitant medication use during the study were documented in the subject CRF.

A) Prior and Concomitant Antidiarrheal Medication (ADM) Use

The use of ADM was prohibited throughout the Screening phase, randomization visit, and PC phase. However, ADM use was permitted as needed during the PF extension phase.

Table 2 presents a summary of ADMs previously used by > 5% of all Crofelemer subjects or placebo subjects. A majority of subjects in each treatment group reported prior ADM use to control diarrhea (all Crofelemer: 64%, placebo: 60%). The most common (≥ 25% of Crofelemer subjects or placebo subjects) ADMs used previously were loperamide hydrochloride (Crofelemer: 40%, placebo: 37%) and atropine and diphenoxylate [(Lomotil®) Crofelemer: 26%, placebo: 22%]. Prior ADM use during the 4 weeks before randomization was reported by approximately 40% of subjects (all Crofelemer: 43%, placebo: 38%).

Table 2: Antidiarrheal Medications Previously Used in > 5% of All Crofelemer-Treated Subjects or Placebo-Treated Subjects (ITT Population)

Medication Class Preferred Term	Crofelemer 125 mg BID n (%) (N = 136)	Crofelemer 250 mg BID n (%) (N = 54)	Crofelemer 500 mg BID n (%) (N = 46)	Total Crofelemer n (%) (N = 236)	Placebo BID n (%) (N = 138)
Any ATC Class	79 (58)	38 (70)	34 (74)	151 (64)	83 (60)
Loperamide hydrochloride	49 (36)	26 (48)	19 (41)	94 (40)	51 (37)
Lomotil	31 (23)	18 (33)	12 (26)	61 (26)	30 (22)
Bismuth subsalicylate	10 (7)	2 (4)	3 (7)	15 (6)	12 (9)
Loperamide	4 (3)	4 (7)	6 (13)	14 (6)	9 (7)

From Section 11.2.3 of the Main Study Report, Page 84
Abbreviations: BID = twice daily; and ITT = intent-to-treat.

Table 3 presents a summary of ADMs used as a concomitant medication during the PC phase of the study. Per the protocol, ADM use was prohibited during the Screening and PC phases of the study. As shown in the table, ADM use was infrequent during the PC phase of the trial, and the proportion of subjects who used ADMs during the PC phase was higher in the placebo group compared with the all Crofelemer group. No subjects in the study used ADM for > 3 days in the PC phase.

Table 3: Antidiarrheal Medications Used as a Concomitant Medication During the PC Phase (ITT Population)

Medication Class Preferred Term	Crofelemer 125 mg BID n (%) (N = 136)	Crofelemer 250 mg BID n (%) (N = 54)	Crofelemer 500 mg BID n (%) (N = 46)	Total Crofelemer n (%) (N = 236)	Placebo BID n (%) (N = 138)
Loperamide hydrochloride	1 (< 1)	2 (4)	3 (7)	6 (3)	5 (4)
Lomotil	1 (< 1)	0	2 (4)	3 (1)	2 (1)
Bismuth subsalicylate	1 (< 1)	0	0	1 (< 1)	2 (1)
Loperamide	0	0	1 (2)	1 (< 1)	2 (1)

From Section 11.2.3 of the Main Study Report, Page 85
Abbreviations: BID = twice daily; and ITT = intent-to-treat.

Intermittent, as-needed use of opioid pain medications was prohibited in this study. Only subjects on methadone, buprenorphine, or buprenorphine/naloxone therapy for the purpose of pain management or addiction management that was stable for 3 months and fentanyl patch therapy that was stable for 4 weeks were allowed to enter the study.

The use of antibiotics was prohibited within 2 weeks prior to Screening and during the Screening phase, with the exception of stable antibiotic therapy for prophylactic treatment of infection or an HIV-associated condition for at least 4 weeks prior to screening. Antibiotics were *not* prohibited during the PC phase if deemed necessary by the investigator for treatment of infection.

B) Baseline and Concomitant Antiretroviral Medications Use

Table 4 presents a summary of baseline ART for PC phase, and common (> 10% of any treatment group) concomitant ART used during the PC phase. Per the protocol, subjects were required to be on a stable ART regimen for at least 4 weeks prior to screening and throughout the PC phase.

At baseline, nearly all ITT subjects (> 97%) reported current use of an ART regimen. Most subjects randomized to Crofelemer (68%) or placebo (70%) were receiving protease inhibitors. Likewise, nearly all subjects received ART (> 97%) concomitantly during the PC phase, with the most frequently used ART being protease inhibitors or reverse-transcriptase inhibitors. The most frequently used ART in each group were tenofovir/emtricitabine (all Crofelemer: 35%; placebo: 38%), ritonavir (all Crofelemer: 34%; placebo: 36%), and lopinavir/ritonavir (all Crofelemer: 28%; placebo: 29%).

Table 4: Baseline and Concomitant ART Use in the PC Phase – ITT Population

	Crofelemer Tablets				
	125 mg BID (N = 136) n (%)	250 mg BID (N = 54) n (%)	500 mg BID (N = 46) n (%)	Total Crofelemer (N = 236) n (%)	Placebo BID (N = 138) n (%)
Baseline ART Use					
Reported Current Use of ART					
Yes	135 (99)	52 (96)	45 (98)	232 (98)	134 (97)
No	1 (< 1)	2 (4)	1 (2)	4 (2)	4 (3)
Current Use of Protease Inhibitors					
Yes	87 (64)	41 (76)	33 (72)	161 (68)	97 (70)
No	49 (36)	13 (24)	13 (28)	75 (32)	41 (30)
Common Concomitant ART (>10% of Any Treatment Group)					
Any Concomitant ART	135 (99)	53 (98)	45 (98)	233 (99)	134 (97)
Tenofovir/Emtricitabine (Truvada)	45 (33)	22 (41)	16 (35)	83 (35)	52 (38)
Ritonavir	46 (34)	18 (33)	15 (33)	79 (34)	49 (36)
Continued					
Lopinavir/Ritonavir (Kaletra)	30 (22)	21 (39)	15 (33)	66 (28)	40 (29)

	Crofelemer Tablets				
	125 mg BID (N = 136) n (%)	250 mg BID (N = 54) n (%)	500 mg BID (N = 46) n (%)	Total Crofelemer (N = 236) n (%)	Placebo BID (N = 138) n (%)
Efavirenz/Tenofovir/ Emtricitabine (Atripla)	30 (22)	7 (13)	7 (15)	44 (19)	21 (15)
Tenofovir disoproxil fumarate	18 (13)	8 (15)	5 (11)	31 (13)	14 (10)
Antazanavir sulfate	19 (14)	3 (6)	6 (13)	28 (12)	22 (16)
Abacavir w/ lamivudine	17 (13)	5 (9)	5 (11)	27 (11)	18 (13)
Darunavir	19 (14)	4 (7)	4 (9)	27 (11)	14 (10)
Raltegravir	16 (12)	4 (7)	5 (11)	25 (11)	11 (8)
Valaciclovir hydrochloride	12 (9)	8 (15)	5 (11)	25 (11)	16 (12)
Fosamprenavir	12 (9)	6 (11)	4 (9)	22 (9)	13 (9)
Zidovudine w/ lamivudine	12 (9)	3 (6)	3 (7)	18 (8)	15 (11)
Lamivudine	7 (5)	6 (11)	4 (9)	17 (7)	6 (4)
Nevirapine	8 (6)	6 (11)	3 (7)	17 (7)	9 (7)
Atazanavir	5 (4)	6 (11)	2 (4)	13 (6)	2 (1)

From Section 11.2.4 of the Main Study Report, Page 87
Abbreviations: ART = antiretroviral therapy; BID = twice daily; and ITT = intent-to-treat.
Note: Concomitant medications are presented by descending order of frequency among all Crofelemer-treated subjects within each system organ class.

6 Review of Efficacy

Efficacy Summary

- The efficacy evaluation is based on the placebo-controlled, 4-week two stage study (ADVENT). The results show statistical significance (17.6% vs. 8.0%; p=0.0096; 1-sided compared with 0.025) of Crofelemer treatment (125 mg PO bid) over placebo on the primary endpoint (i.e., the proportion of patients achieving clinical response).
    - The clinical response was defined as ≤ 2 watery bowel movements per week for at least 2 of 4 weeks during the 4-week efficacy assessment period (i.e., the PC phase). Since the patients had at least 5 days of watery bowel movements during the 7-day Screening period prior to randomization, the clinical response represents an improvement in HIV diarrhea for at least 50% of the time.

- The subgroup of patients with persistent diarrhea despite the use of prior ADMs had a higher treatment difference (Crofelemer 125 mg BID vs. placebo) for the primary endpoint (clinical response) than the subgroup of patients who had no prior use of ADMs (treatment difference of 14.6% in the subgroup with any prior ADM use vs. 1.9% in the subgroup with no prior ADM use). It should be noted that the treatment difference observed in the subgroup of patients that used 1 ADM previously and the treatment difference observed in the subgroup of patients that used 2 or more ADMs previously was 6.9% and 27.6%, respectively.

- The subgroup of patients with concomitant protease inhibitor (PI) use had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients with no concomitant PI use (11.0% vs. 6.2%).

- The subgroup of patients with CD4 cell counts < 404 cells/mm^3 had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients with CD4 cell counts ≥ 404 cells/mm^3 (15.6% vs. 7.2%).

- The subgroup of patients with > 2 watery BM's per day had a similar treatment difference for the primary endpoint (clinical response) as the subgroup of patients with ≤ 2 watery BM's per day (9.6% vs. 8.2%).

- The subgroup of patients with duration of diarrhea > 2 years had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients with duration of diarrhea ≤ 2 years (11.1% vs. 6.9%).

- The subgroup of patients that had been diagnosed with HIV for > 12 years had a numerically higher treatment difference for the primary endpoint (clinical response) than the subgroup of patients that had been diagnosed with HIV for ≤ 12 years (14.1% vs. 5.5%).

In the 20-week PF phase, both the patients that crossed over from placebo and the patients that continued on Crofelemer appeared to show a persistent anti-diarrheal effect.

Taken together, the exploratory subgroup analyses and the results of the PF phase support the finding that Crofelemer treatment may address the unmet medical needs of HIV/AIDS patients.

In addition, there is supportive data from two studies (37554-210 and 37554-209) using a different formulation and a different primary endpoint (change from baseline in daily stool weight during the in-patient periods; Crofelemer N = 345 vs. Placebo N = 140). The results were supportive to Study ADVENT.

6.1 Indication

The proposed indication is:

> "…for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy."

6.1.1 Methods

Determination of efficacy is based on the primary efficacy endpoint:

> The proportion of patients in the Intent-to-Treat (ITT) population who experienced clinical response (defined as ≤ 2 watery bowel movement per week for at least 2 of 4 weeks during the 4-week efficacy assessment period).

Secondary efficacy endpoints during the 4-week efficacy assessment period were as follows:

- Number of watery bowel movements per day;
- Daily stool consistency score;
- Daily abdominal pain or discomfort score;
- Number of days per week that subjects experienced urgency;
- Number of days per week that subjects experienced fecal incontinence;
- Number of bowel movements per day; and

- Proportion of subjects undergoing an unscheduled visit for a significant worsening or clinically significant exacerbation of diarrhea.

6.1.2 Demographics

Table 5 summarizes demographic characteristics for the ITT population in the PC phase of ADVENT. The table presents demographics for all subjects (Stage 1 + Stage 2) and for Stage 1 and Stage 2 independently. In the combined analysis, demographic characteristics were similar between treatment groups in the PC phase of the trial. Most subjects (≥ 84%) in each treatment group were male. Mean and median age in the Crofelemer groups and the placebo group was approximately 45 years, and all but 2 subjects in the study were < 65 years old. The Crofelemer 250 mg and 500 mg groups had higher percentages of White subjects and lower percentages of Black subjects compared with the Crofelemer 125 mg group and the placebo group. This difference in distribution was due to a higher percentage of Black subjects enrolled into the125 mg group (42% vs. 27%) and the placebo group (44% vs. 28%) in Stage 2 of the study compared with Stage 1 (Table 5). Demographic trends were similar in the Safety population for the PC and PF phases of the study.

Table 5: Demographics – PC Phase (ITT Population)

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)

(Continued)

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)

From Section 11.2 of the Main Study Report, Page 81
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.

Baseline Characteristics

Diarrhea Characteristics

Table 6 presents a summary of key baseline diarrhea characteristics for the ITT population in the PC phase. The table summarizes these parameters for each study stage and for Stage 1 and 2 combined.

In the combined analysis (Stage 1 + Stage 2), the mean time since onset of diarrhea ranged between 5 and 7 years in each treatment group, and the primary causes of diarrhea in all Crofelemer- and placebo-treated patients were ART (71% and 75%, respectively) and HIV infection (26% and 24%, respectively). Baseline averages for daily bowel movements (watery, loose, and total) during the 7 days prior to first dose of study drug were comparable between treatment groups. For example, mean daily numbers of total bowel movements were 5.2 (all Crofelemer subjects) and 5.6 (placebo group), mean daily number of loose bowel movements were 1.8 (Crofelemer) and 1.8 (placebo), and mean daily number of watery bowel movements were 2.7 (Crofelemer) and 3.0 (placebo).

Baseline diarrhea symptom scores for stool consistency and abdominal pain were similar between the Crofelemer treatment groups and the placebo group. Of note, mean abdominal pain scores at baseline were consistent with only mild abdominal pain and discomfort in the trial, with scores ≤ 1.03 in each treatment group. In addition, Crofelemer- and placebo-treated patients had a similar mean number of days per week with urgency (Crofelemer: 5.2 vs. placebo: 5.3) and fecal incontinence (Crofelemer: 2.9 vs. placebo: 3.1) at baseline.

By stage, there was a statistically significant overall difference (Crofelemer plus Placebo) between Stage 1 and Stage 2 (3.2 vs. 2.7, p = 0.0348) in baseline daily watery bowel movements for the ITT population. This between-stage difference was primarily due to a greater mean number of daily watery bowel movements at baseline in Stage 1 in the placebo group (3.5 vs. 2.8; p = 0.0443). Baseline daily watery bowel movements were more comparable across study stages in the Crofelemer 125 mg bid group (2.9 in Stage 1 versus 2.6 in Stage 2; p = 0.4575).

In addition, the mean number of years since diarrhea started was longer for patients in Stage 1 compared with subjects in Stage 2 for both the 125 mg bid Crofelemer group (6.8 vs. 5.5) and the placebo group (7.7 vs. 5.8). A higher proportion of patients in Stage 1 also had diarrhea caused by HIV infection compared with patients in Stage 2 (125 mg bid: 32% vs. 20%; placebo: 36% vs. 17%); conversely, a higher proportion of patients had diarrhea caused by ART in Stage 2 compared with Stage 1.

Trends for baseline diarrhea characteristics were similar in the Safety population for the PC and PF phases of the study.

Table 6: Baseline Diarrhea Characteristics - PC Phase (ITT Population)

	Crofelemer Tablets			Total Crofelemer	Placebo BID
	125 mg BID	250 mg BID	500 mg BID		
Combined (Stage I + Stage II)					
N	**136**	**54**	**46**	**236**	**138**
Time Since Diarrhea Started (Years)					
Mean (SD)	5.9 (5.77)	5.5 (4.89)	6.9 (5.91)	6.0 (5.61)	6.5 (6.51)
Median (Min, Max)	3.5 (0.1, 24.5)	5.1 (0.2, 20.9)	6.1 (0.2, 22.2)	4.5 (0.1, 24.5)	4.1 (0.1, 32.4)
Cause of Diarrhea – n (%)					
Antiretroviral Therapy	102 (75)	37 (69)	29 (63)	168 (71)	104 (75)
HIV infection of intestine	32 (24)	15 (28)	15 (33)	62 (26)	33 (24)
Other	2 (2)	2 (4)	2 (4)	6 (3)	1 (1)
Daily Watery Bowel Movements[a]					
Mean (SD)	2.7 (1.65)	2.7 (1.47)	2.6 (1.28)	2.7 (1.54)	3.0 (2.08)
Median (Min, Max)	2.3 (0.4, 7.9)	2.2 (0.9, 8.0)	2.4 (0.7, 7.5)	2.4 (0.4, 8.0)	2.6 (0.9, 15.3)
Stool Consistency Score[b]					
Mean (SD)	4.4 (0.41)	4.4 (0.34)	4.3 (0.35)	4.4 (0.38)	4.4 (0.40)
Median (Min, Max)	4.4 (3.1, 5.0)	4.5 (3.3, 5.0)	4.3 (3.6, 5.0)	4.4 (3.1, 5.0)	4.4 (3.0, 5.0)
Stage I					
N	**44**	**54**	**46**	**144**	**50**
Time Since Diarrhea Started (Years)					
Mean (SD)	6.8 (6.43)	5.5 (4.89)	6.9 (5.91)	6.3 (5.71)	7.7 (7.93)
Median (Min, Max)	5.4 (0.1, 24.5)	5.1 (0.2, 20.9)	6.1 (0.2, 22.2)	5.3 (0.1, 24.5)	4.2 (0.1, 32.4)
Cause of Diarrhea – n (%)					
Antiretroviral Therapy	29 (66)	37 (69)	29 (63)	95 (66)	31 (62)
HIV infection of intestine	14 (32)	15 (28)	15 (33)	44 (31)	18 (36)
Other	1 (2)	2 (4)	2 (4)	5 (34)	1 (2)
Daily Watery Bowel Movements[a]					
Mean (SD)	2.9 (1.62)	2.7 (1.47)	2.6 (1.28)	2.7 (1.46)	3.5 (2.68)
Median (Min, Max)	2.6 (0.7, 7.7)	2.2 (0.9, 8.0)	2.4 (0.7, 7.5)	2.4 (0.7, 8.0)	2.7 (1.1, 15.3)
Stool Consistency Score[b]					
Mean (SD)	4.4 (0.42)	4.4 (0.34)	4.3 (0.35)	4.4 (0.37)	4.4 (0.40)
Median (Min, Max)	4.5 (3.3, 5.0)	4.5 (3.3, 5.0)	4.3 (3.6, 5.0)	4.4 (3.3, 5.0)	4.5 (3.0, 5.0)
Stage II					
N	**92**				**88**
Time Since Diarrhea Started (Years)					
Mean (SD)	5.5 (5.42)				5.8 (5.48)
Median (Min, Max)	3.3 (0.2, 20.4)				4.0 (0.1, 23.0)
Cause of Diarrhea – n (%)					
Antiretroviral Therapy	73 (79)				73 (83)
HIV infection of intestine	18 (20)				15 (17)
Other	1 (1)				0

Continued

	Crofelemer Tablets			Total Crofelemer	Placebo BID
	125 mg BID	250 mg BID	500 mg BID		
Daily Watery Bowel Movements[a]					
Mean (SD)	2.6 (1.67)				2.8 (1.67)
Median (Min, Max)	2.2 (0.4, 7.9)				2.4 (0.9, 9.7)
Stool Consistency Score[b]					
Mean (SD)	4.4 (0.41)				4.4 (0.40)
Median (Min, Max)	4.4 (3.1, 5.0)				4.4 (3.1, 5.0)

From Section 11.2.3 of the Main Study Report, Page 83

Abbreviations: BID = twice daily; HIV = human immunodeficiency virus; ITT = intent-to-treat; SD = standard deviation.
[a] Baseline was the average of daily data from the 7 days prior to first dose day of study drug.
[b] Baseline was the average of daily stool consistency scores from the 7 days prior to first dose day of study drug. The daily score = (1*# of vary hard stools + 2*# of hard stools + 3*# of formed stools + 4*# of loose stools +5*# of watery stools)/(# of total stools).

HIV Characteristics

Table 7 summarizes baseline HIV characteristics for the ITT population in the PC phase. In the combined analysis (Stage 1 + Stage 2) the treatment groups were balanced with respect to baseline HIV characteristics. The mean time since first diagnosis of HIV was approximately 12-13 years in each treatment group, and ≥ 96% of patients in each group reported use of ART. Mean (SD) CD4 cell count was 477.9/μL (240.3) and 530.5/μL (244.8) in all Crofelemer subjects and placebo subjects, respectively. Most patients in each treatment group (≥ 78%) had no HIV RNA detected at baseline. A high viral load (> 1000 HIV copies/mL) was recorded in 7% of all Crofelemer patients and 7% of placebo patients. Similar trends were observed for each study stage for the ITT population. Baseline HIV characteristics were also similar in the Safety population for both the PC and PF phases of the study.

Table 7: Baseline HIV Characteristics - PC Phase (ITT Population)

	Crofelemer Tablets			Total Crofelemer	Placebo BID
	125 mg BID	250 mg BID	500 mg BID		
Combined (Stage I + Stage II)					
N	**136**	**54**	**46**	**236**	**138**
Time Since First Diagnosis of HIV (Years)					
Mean (SD)	12.4 (6.32)	13.1 (6.71)	13.2 (5.82)	12.7 (6.30)	12.4 (7.52)
Median (Min, Max)	11.7 (0.3, 29.3)	13.3 (1.3, 24.0)	13.5 (1.4, 24.7)	12.6 (0.3, 29.3)	12.3 (0.3, 29.8)
CD4 Cell Count (cells/µL)					
Mean (SD)	497.5 (231.7)	425.2 (226.1)	481.7 (275.2)	477.9 (240.3)	530.5 (244.8)
< 404 – n (%)	55 (40)	29 (54)	21 (46)	105 (45)	39 (28)
≥ 404– n (%)	81 (60)	25 (46)	25 (54)	131 (56)	99 (72)
HIV Viral Load (HIV copies/mL) – n (%)					
< 400 No RNA Detected	111 (82)	44 (82)	36 (78)	191 (80)	116 (84)
< 400 RNA Detected	13 (10)	4 (7)	5 (11)	22 (9)	10 (7)
400 – 9999	6 (4)	0	1 (2)	7 (3)	3 (2)
≥ 1000	6 (4)	6 (11)	4 (9)	16 (7)	9 (7)
Stage I					
N	**44**	**54**	**46**	**144**	**50**
Time Since First Diagnosis of HIV (Years)					
Mean (SD)	12.5 (5.79)	13.1 (6.71)	13.2 (5.82)	12.9 (6.12)	13.1 (7.22)
Median (Min, Max)	12.9 (2.6, 24.5)	13.3 (1.3, 24.0)	13.5 (1.4, 24.7)	13.3 (1.3, 24.7)	15.2 (1.4, 26.7)
CD4 Cell Count (cells/µL)					
Mean (SD)	486.0 (236.7)	425.2 (226.1)	481.7 (275.2)	461.8 (245.8)	534.3 (236.6)
< 404 – n (%)	17 (39)	29 (54)	21 (46)	67 (47)	13 (26)
≥ 404– n (%)	27 (61)	25 (46)	25 (54)	77 (54)	37 (74)
HIV Viral Load – n (%)					
< 400 No RNA Detected	38 (86)	44 (82)	36 (78)	118 (82)	36 (72)
< 400 RNA Detected	3 (7)	4 (7)	5 (11)	12 (8)	6 (12)
400 – 9999	1 (2)	0	1 (2)	2 (1)	1 (2)
≥ 1000	2 (5)	6 (11)	4 (9)	12 (8)	7 (14)
Stage II					
N	**92**				**88**
Time Since First Diagnosis of HIV (Years)					
Mean (SD)	12.3 (6.59)				11.9 (7.69)
Median (Min, Max)	11.4 (0.3, 29.3)				11.0 (0.3, 29.8)
CD4 Cell Count (cells/µL)					
Mean (SD)	503.0 (230.4)				528.4 (250.7)
< 404 – n (%)	38 (41)				26 (30)
≥ 404– n (%)	54 (59)				62 (71)
HIV Viral Load – n (%)					
< 400 No RNA Detected	73 (79)				80 (91)
< 400 RNA Detected	10 (11)				4 (5)
400 – 9999	5 (5)				2 (2)
≥ 1000	4 (4)				2 (2)

From Section 11.2.3 of the Main Study Report, Page 83
Abbreviations: BID = twice daily; HIV = human immunodeficiency virus; ITT = intent-to-treat; SD = standard deviation.

6.1.3 Subject Disposition

Subject Disposition by Stage and Phase:
In total, 376 patients were randomized to receive Crofelemer (N=238) or placebo (N=138) in the study.

- In Stage 1, 196 patients were randomized to a Crofelemer dose group (N=146) or to the placebo group (N=50). Crofelemer-treated patients in Stage 1 were randomized to 125 mg bid (N=45), 250 mg bid (N=54), or 500 mg bid (N=47).

- In Stage 2, 92 subjects were randomized to Crofelemer 125 mg bid and 88 patients were randomized to placebo.

Subject Disposition by Phase:

- PC phase: Most patients in each treatment group (> 85%) in the study completed the PC phase. A total of 18 patients (8%) treated with Crofelemer prematurely discontinued during the PC phase; the most frequent reasons for discontinuation for Crofelemer subjects were withdrawal of consent (8 patients), subject loss to follow-up (6 patients), and noncompliance with study medication (2 patients). Nine patients (7%) randomized to placebo prematurely discontinued; the most frequent reasons for discontinuation for placebo subjects were AE (3 patients) and exacerbation of diarrhea (2 patients). Twelve patients completed the PC phase of the study, but discontinued prior to starting the PF phase.

- PF phase: In the PF phase, 337 subjects were treated with Crofelemer in the following dose groups: 125 mg bid (N=220), 250 mg bid (N=67), and 500 mg bid (N=50). Of these patients, 126 had received placebo in the double-blind PC phase. In total, 274 patients (81%) completed the PF phase and 63 patients (19%) discontinued early. The primary reasons for early discontinuation were withdrawal of consent (22 patients), loss to follow-up (12 patients), and other (10 patients).

Subject disposition is summarized in Table 8 for all randomized patients for the PC and PF phases. Patients in the table are presented by treatment group, and combining Stage 1 and Stage 2.

Table 8: Subject Disposition by Phase: Randomized Patients in Stage 1 + Stage 2

	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)	

From Section 10.1 of the Main Study Report, Page 75
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 patients 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 patient (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) Issued (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) patients in the PF phase of Stage 1 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.

Discussion:
There were no notable differences between Stage 1 and Stage 2 in the completion rate or early discontinuation rate for either the PC phase or the PF phase.

Datasets Analyzed

Three populations were used for study analyses:

- the ITT population,
- the PP population, and
- the Safety population.

These populations are summarized by treatment group in Table 9.

ITT population: In total, 374 of 376 randomized subjects received study medication and were included in the ITT population; 2 subjects randomized to Crofelemer (Subjects 0021-0009 and 0032-0003) did not take randomized study drug and were excluded.

PP population: Most randomized subjects in each treatment group (≥ 94%) were also included in the PP population.

Safety population: A total of 226 of 238 Crofelemer-treated subjects (95%) and 137 of 138 placebo-treated subjects (99%) were included in the Safety population. Twelve subjects in the Crofelemer groups and 1 subject in the placebo group did not have a post-baseline safety assessment recorded in the study and were excluded. Two of the 12 Crofelemer subjects excluded from the Safety population did not take study drug.

Table 9: Analysis Populations by Treatment Group (Randomized Subjects)

Population	Crofelemer 125 mg BID (N = 137) n (%)	Crofelemer 250 mg BID (N = 54) n (%)	Crofelemer 500 mg BID (N = 47) n (%)	Placebo BID (N = 138) n (%)
Randomized (N)	**137**	**54**	**47**	**138**
ITT population[a]	136 (99)	54 (100)	46 (98)	138 (100)
PP population	130 (95)	51 (94)	44 (94)	135 (98)
Reasons for exclusion				
< 5 days of watery stools at baseline[b]	5 (4)	1 (2)	1 (2)	1 (1)
Pathogen in stool related to diarrhea at screening	1 (1)	2 (4)	0	1 (1)
Violated exclusion criterion #11[c]	0	0	1 (2)	0
Violated exclusion criterion #16[d]	0	0	0	1 (1)
Safety population[e]	130 (95)	54 (100)	42 (89)	137 (99)
Reasons for exclusion				
Not treated	1 (1)	0	1 (2)	0
No postbaseline safety assessment	7 (5)	0	5 (11)	1 (1)

From Section 11.1 of the Main Study Report, Page 79
Abbreviations: BID = twice daily; ITT = Intent-to-Treat; and PP = per protocol.
a. The ITT population included all randomized subjects who took at least 1 dose of randomized study drug. Two subjects (0021-0009, 0032-0003) did not take any randomized study drug and were excluded.

b. Enrolled subjects were required to have at least 1 or more watery bowel movements per day on at least 5 of the last 7 days of the screening phase.
c. Exclusion criterion #11: Evidence on prior colonoscopy or upper endoscopy of colitis, enteritis, infection (HIV associated or otherwise), or neoplasm, other than benign polyps.
d. Exclusion criterion #16: History of ulcerative colitis, Crohn's disease, celiac sprue (gluten-enteropathy), chronic pancreatitis, malabsorption, or any other gastrointestinal disease associated with diarrhea.
e. The Safety population included subjects who received at least 1 dose of randomized study drug and had at least 1 post-baseline assessment.

Protocol Deviations

Major protocol deviations during the PC phase were defined prospectively as:

- deviation of major study selection criteria;
- unblinding of treatment by emergency measures; and
- discovery of a pathogen in a stool sample during screening or baseline which appeared related to worsening diarrhea.

Eleven Crofelemer subjects (125 mg bid: 6 subjects; 250 mg bid: 3 subjects; and 500 mg bid: 2 subjects) and 3 placebo subjects had major protocol deviations in the study.

The most frequent major protocol deviations in the study were subject enrollment despite < 5 days of watery stools at baseline (Crofelemer: 7 subjects, placebo: 1 subject) and subject enrollment despite the detection of a pathogen in the stool related to diarrhea at screening or baseline (Crofelemer: 3 subjects, placebo: 1 subject). In addition, 1 Crofelemer-treated subject was in violation of Exclusion Criterion #11 at baseline (i.e., evidence on prior colonoscopy or upper endoscopy of colitis, enteritis, infection, or neoplasm, other than benign polyps), and 1 placebo-treated subject was in violation of Exclusion Criterion #16 at baseline (i.e., history of ulcerative colitis, Crohn's disease, celiac sprue, chronic pancreatitis, malabsorption, or any other gastrointestinal disease associated with diarrhea).

6.1.4 Analysis of Primary Endpoint

The primary endpoint of Study ADVENT was clinical response, defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the PC phase. The primary endpoint was designed to compare the optimal dose of Crofelemer (as identified by the IAC) versus placebo by combining results from Stage 1 and Stage 2.

Patients in the study had at least 1 or more watery bowel movements per day on ≥ 5 of the last 7 days of the placebo screening phase. Thus, clinical response represented an improvement of diarrhea at least 50% of the time. This endpoint was clinically relevant because the diarrhea experienced by patients with HIV/AIDS can have a major impact on subjects' quality of life (Hill, 2009; Siddiqui, 2007; Call, 2000; Kartalija, 1999). Primary efficacy assessments are based on the adaptive design. Treatment group

comparison for the primary endpoint was 1-sided with a significance level of 0.025 using the methods of Posch and Bauer (Posch, 2005).

Primary Endpoint - Combined Analysis (Stage 1 + Stage 2)

Table 10 presents results for the primary endpoint comparing Crofelemer 125 mg bid with placebo. The primary endpoint, clinical response, was experienced by a statistically significantly larger proportion of patients in the Crofelemer 125 mg bid group compared with the placebo group in the ITT population (17.6% vs. 8.0%, 1-sided p = 0.0096).

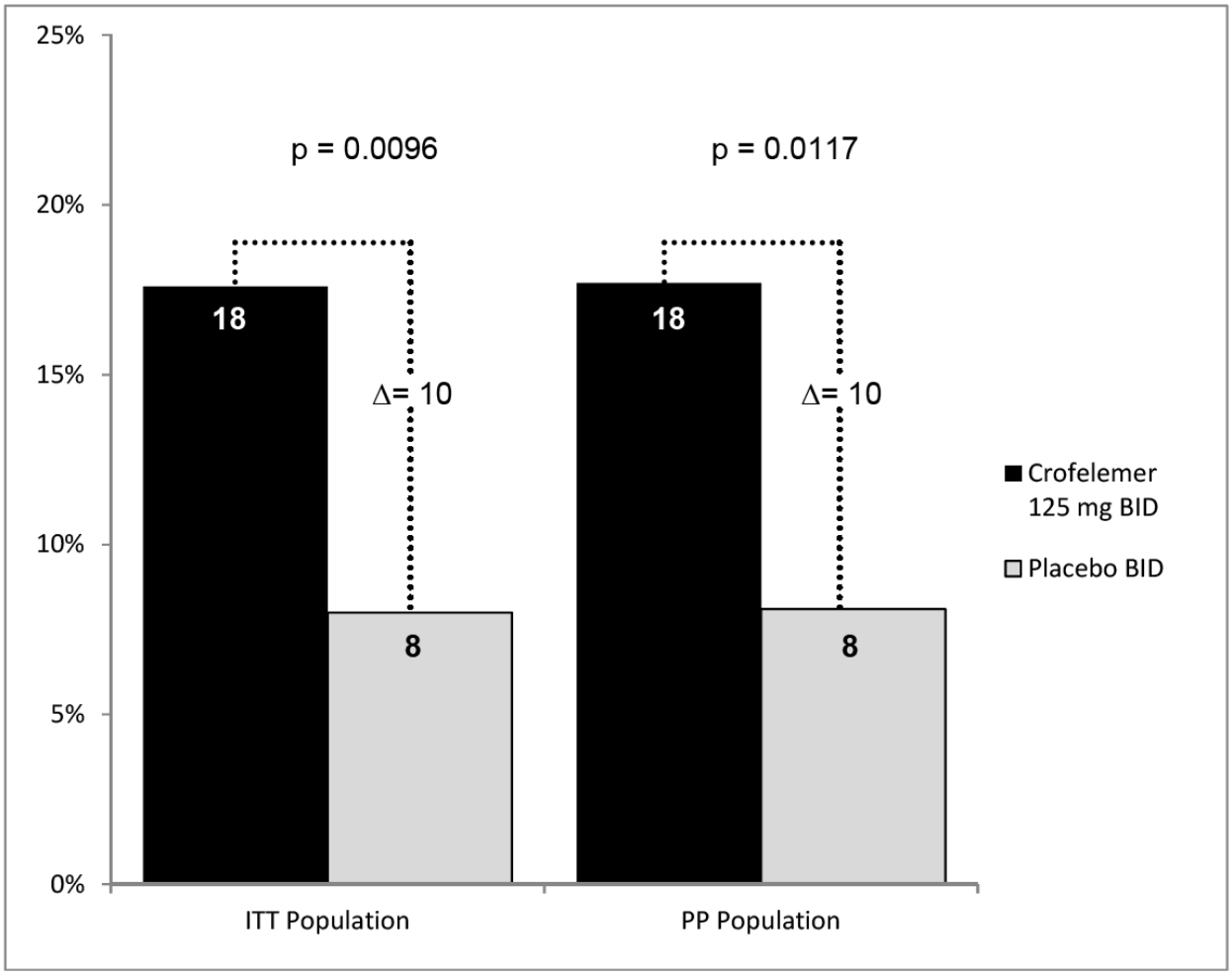
Table 10: Clinical Response: By Stage and Combined (ITT Population)

Stage 1:				**Stage 2:**	
125 mg	250 mg	500 mg	**Placebo**	**125 mg**	**Placebo**
20.5% (9/44)	9.3% (5/54)	19.6% (9/46)	**2.0%** (1/50)	**16.3%** (15/92)	**11.4%** (10/88)
Δ=**18.5%**	Δ=7.3%	Δ=17.6%	--	Δ=**4.9%**	--

Combined Analysis[a,b]:	
125 mg	**Placebo**
17.6% (24/136)	**8.0%** (11/138)
Δ=**9.6%** (p=0.0096)	--

From Section 11.4.1 of the Main Study Report
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-value was 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.

Figure 5: Primary Endpoint – Percent of Subjects with Clinical Response (Crofelemer 125 mg bid vs. Placebo) – ITT and PP Populations



From Section 11.4.1 of the Main Study Report, Page 92
Notes: Clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the placebo-controlled treatment phase. P-values and CIs were calculated based on the methods of Posch and Bauer.

Stage 1 – Primary Endpoint

Table 11 presents a summary of clinical response in Stage 1. A higher percentage of patients in each of the Crofelemer groups experienced clinical response compared with the placebo group. The 125 mg bid and 500 mg bid Crofelemer dose groups performed similarly in Stage 1 and the treatment difference versus placebo was statistically significant using the methods of Posch and Bauer (Posch, 2005): 125 mg bid (1-sided p = 0.0019) and 500 mg bid group compared with placebo (1-sided p = 0.0024). A

numerically, but not statistically significantly higher, proportion of patients observed to respond to Crofelemer treatment in the 250 mg bid group (1-sided p = 0.0563).

Table 11: Stage 1 Clinical Response (ITT Population)

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	---

From Section 11.4.1 of the Main Study Report, Page 93
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.

Stage 1 Stool Consistency

A dose-response trend suggesting improved stool consistency was observed in Stage 1 in a responder analysis for stool consistency. This responder analysis is presented in Table 12 and was performed using the same statistical methods as the primary endpoint. A stool consistency responder was defined as a subject with an average stool consistency score < 4 for at least 2 of the 4 weeks of the PC phase.

Stool consistency was scored for each bowel movement in the study as follows: 1=very hard, 2=hard, 3=formed, 4=loose, 5=watery. At baseline, mean daily stool consistency scores ranged from 4.3 to 4.4 in the treatment groups (see Table 10), consistent with loose and watery stools. Therefore, a score < 4 was consistent with improvement to more formed stools.

The proportion of stool consistency responders in Stage 1 was 22% in the placebo group, 32% in the Crofelemer 125 mg bid group, 37% in the Crofelemer 250 mg bid group, and 50% in the Crofelemer 500 mg bid group. An increase in dose resulted in an increase in stool consistency response with statistical significance versus placebo in the Crofelemer 500 mg bid group (Δ = 28%, 1-sided p = 0.0021). This dose response trend was statistically significant using a Cochran-Armitage trend test (p = 0.039).

Table 12: Stage 1 Stool Consistency Response[a] (ITT Population)

Parameter / Statistic	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo n (%)
Responder – n/N (%)	14/44 (31.8%)	20/54 (37.0%)	23/46 (50.0%)	11/50 (22.0%)
Treatment Difference	9.8%	15.0%	28.0%	---
1-Sided 97.5% CI[b]	[-8.1%, ∞)	[-2.6%, ∞)	[8.8%, ∞)	---
1-Sided p-value (Versus Placebo)[b]	0.1412	0.0470	0.0021	---
Dose Response p-value[c]			0.039	

From Section 11.4.1 of the Main Study Report, Page 94
Abbreviations: BID = twice daily; CI = confidence interval; ITT = intent-to-treat.
Note: Daily stool consistency score = [1*(# of very hard stools) + 2*(# of hard) + 3*(# of formed) + 4*(# of loose) +5*(# of watery) / (# of stools). Baseline was the average daily stool consistency score during the 7 days prior to the first dose of randomized study drug. Post-baseline was the average daily stool consistency score during the 28-day placebo-controlled phase.
a. Stool consistency response was defined as an average stool consistency score < 4 for at least 2 of the 4 efficacy assessment weeks in the PC phase.
b. P-values and CIs were calculated based on the methods of Posch and Bauer (2005).
c. P-value was calculated from Cochran-Armitage Trend Test.

Interim Analysis and Dose Selection

Stage 1 data for clinical response were evaluated in an interim analysis as part of the adaptive study design. Following completion of Stage 1, an Interim Analysis Report was prepared by an independent statistician and an independent analysis committee (IAC) selected the optimal dose regimen for comparison to placebo in the primary efficacy analysis. The IAC subsequently prepared a Dose Selection Report.

Table 13 summarizes the percentage of patients with clinical response in Stage 1 as presented in the Dose Selection Report. Findings from the interim analysis showed the highest percentage of responders in the Crofelemer 125 mg bid group (20%), and the lowest percentage of responders in the placebo group (12%).

The number of clinical responders in the interim analysis differs from results obtained from the final analysis of Stage 1. Seven patients (Crofelemer: 2, placebo: 5) were responders in the interim analysis, but were not responders in the final analysis, and 1 patient (Crofelemer) was a responder in the final analysis but not the interim analysis. The reasons for these discrepancies were as follows:

- The interim analysis did not take into account the use of prohibited medications from the CRF in determining clinical responders; therefore, 3 placebo subjects (0003-0014, 0007-0029, and 0012-0003) were responders in the interim analysis but not the final analysis. Per Section 9.2.1 of the Protocol and Section 5.3 of the Statistical Analysis Plan (SAP), subjects who used prohibited medications (i.e., ADM or opiate pain medication), for > 3 days in the PC phase were non-responders. For the interim analysis, only the data from the IVRS was used to determine prohibited medication use. The final analysis used the CRFs and the

IVRS to ascertain prohibited medication use from all sources, including medications collected during study site visits and telephone contacts.

- The interim analysis included the first 3 days of randomized study drug in the analysis. Per the protocol and the SAP, the first 3 days of the PC phase were a run-in period and not part of efficacy assessments. Therefore, 2 placebo subjects (0030-0006 and 0044-0006) and 2 Crofelemer 250 mg bid subjects (0009-0006 and 0012-0004) were considered responders in the interim analysis but not the final analysis. In addition, 1 Crofelemer subject in the 500 mg bid group (0031-0003) was considered a responder in the final analysis but not in the interim analysis.

Despite these discrepancies, both the interim and final analyses of Stage 1 showed that the highest percentage of clinical responders was in the Crofelemer 125 mg bid group. Based upon the criteria for dose selection outlined in the Interim Analysis Charter, the Crofelemer 125 mg bid dose was the appropriate dose for selection for Stage 2 using either the interim or final analysis results.

Table 13: Interim Analysis Results: Percent of Subjects with Clinical Response

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)

From ADVENT Dose Selection Report. Page 95
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.

Stage 2 – Primary Endpoint

Table 14 presents a summary of clinical response in Stage 2 for the Crofelemer 125 mg bid group and the placebo group. There was a numerically higher proportion of clinical responders with Crofelemer 125 mg bid versus placebo in Stage 2; however, the treatment difference was not statistically significant (p = 0.1690).

Table 14: Stage 2 Clinical Response[a] (ITT Population)

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	--

From Section 11.4.1 of the Main Study Report, Page 96
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.

Discussion of Clinical Response in Stage 1 vs. Stage 2

The proportion of clinical responders in the Crofelemer 125 mg bid group was generally consistent in Stages 1 and 2 (20.5% and 16.3%, respectively). Placebo-treated subjects, however, had a notably higher proportion of clinical responders in Stage 2 (11.4%) compared with Stage 1 (2.0%).

To understand this difference, an analysis was conducted by the Applicant to determine if important baseline disease characteristics were comparable between study stages. The analysis revealed that Stage 1 and Stage 2 were not comparable at baseline due to a statistically significant imbalance between stages for the number of daily number of watery bowel movements (p = 0.0348; Table 15). This unbalanced distribution was driven by the placebo group, which had a significantly greater mean number of daily watery bowel movements at baseline in Stage 1 versus Stage 2 (3.5 vs. 2.8; p = 0.0443). In contrast, the Crofelemer 125 mg bid group had a comparable baseline daily number of watery bowel movements in Stages 1 and 2 (2.9 and 2.6, respectively; p = 0.4575). As the daily number of watery bowel movements was integral for defining clinical response in the study, the Applicant believes that the unbalanced distribution in the placebo group was the most likely factor contributing to the disparity in placebo responders between stages.

Table 15: Unbalanced Distribution of Daily Watery Bowel Movements at Baseline in Stage 1 Versus Stage 2 – (ITT Population)

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	

From Section 11.4.1 of the Main Study Report, Page 97
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.

To understand the impact of this disparity on study outcomes, baseline daily watery bowel movements were divided into 2 categories by the investigators for comparison: subjects with ≤ 2 daily watery bowel movements and subjects with > 2 daily watery bowel movements. The investigators proposed that subjects with > 2 may have clinically significant diarrhea (DuPont, 1997; Guerrant, 2001; Scheidler, 2001; Schiller, 2000).

The analysis by the Applicant showed that the treatment difference was in favor of Crofelemer 125 mg bid as compared with placebo in subjects who began the study with > 2 daily watery bowel movements (12% vs. 2%, p = 0.0260).

Thus, the Applicant stated that the between-stage imbalance in baseline watery bowel movements may explain why the Crofelemer treatment difference was statistically significant in Stage 1, but not in Stage 2. The statistically significant result in favor of Crofelemer in the combined analysis (primary endpoint) was likely due to Crofelemer's greater treatment effect across study stages in patients with more clinically significant diarrhea.

Table 16: Clinical Responders by Number of Daily Watery Stools (≤ 2 or > 2) at Baseline – Crofelemer 125 mg BID vs. Placebo (ITTPopulation)

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

From Section 11.4.1 of the Main Study Report, Page 98
Abbreviations: BID = twice daily; and ITT = intent-to-treat.
a. P-values were obtained using Fisher's exact test.

Medical Officer Comments:
(1) The adaptive design allows the Applicant to use the combined efficacy data as the pre-specified analysis. Therefore, the final efficacy assessment is based on the combined efficacy data from the PC phases of two Stages.

(2) The reviewer agrees with the Applicant in that Crofelemer may have better effect on the clinically more significant diarrhea. However, this does not explain why Stage 2 placebo had greater spontaneous recovery rate than the Stage 1 placebo (2% vs. 11.4%). This disparity in placebo groups may be affected by the following three factors:

(a) The Applicant did not follow the recommendation by American Gastroenterological Association (AGA) regarding conduct of repeat stool tests (at least 3 times) to exclude the non-HIV infectious diarrhea prior to the study (Wilcox, 1996). As a result, the infectious etiologies may play a role in the spontaneous recovery or improvement of diarrhea, especially in the placebo groups. This is because when CD4 cells > 200, the infectious diarrhea can be spontaneously recovered or improved (Call, 2000).

(b) In Study ADVENT, both the mean CD4 cell counts and the number of patients with category CD4 counts ≥ 404 are higher in the placebo groups as compared with the Crofelemer group.

For example, the placebo patients of Stage 2 had 12% higher of CD4 cell counts ≥ 404 category (immune competent patients) at baseline as compared with the Crofefemer group. More immune competent patients at baseline may lead to the higher spontaneous recovery at the end of the Stage 2 PC phase.

(c) HIV enterocolitis diarrhea is caused by HIV infection. Concomitant ART inhibits HIV replication, therefore may improve HIV enterocolitis and diarrhea.

In summary, the potential spontaneous recovery may mask the efficacy signal of Crofelemer treatment in Study ADVENT. The exploratory subgroup analyses suggest that there may be a higher treatment difference in ADM non-responder, protease-inhibitor user, immune compromised patients, and long-lasting diarrhea patients.

Key Subgroup Analysis of ADVENT: Clinical Response by Prior ADM Use

The subgroup analyses were exploratory, but requested in a meeting prior to the study. The analyses were used as a guide to identify the responsive subgroups (Fisher's exact test). At baseline approximately 60% of patients in both the Crofelemer 125 mg bid group and the placebo group reported prior use of ADM.

As shown in Table 17, the subgroup of patients with persistent diarrhea despite the use of prior ADMs had a numerically higher treatment difference than the subgroup of the patients who had no prior use of ADMs (14.6% vs. 1.9%). The treatment difference observed in the subgroup of patients that used 1 ADM previously and the treatment difference observed in the subgroup of patients that used 2 or more ADMs previously was 6.9% and 27.6%, respectively.

Table 17: Clinical Response by Prior ADM Use (ITT Population)

Subgroup	Crofelemer 125 mg	Placebo	Δ
No prior ADM use	17.0% (9/53)	15.1% (8/53)	1.9%
Any prior ADM use	18.1% (15/83)	3.5% (3/85)	14.6%
1 ADM used previously	13.0% (7/54)	6.1% (3/49)	6.9%
≥ 2 ADM used previously	27.6% (8/29)	0.0% (0/36)	27.6%

From Table 14.2.1.18, Section 14.2 of the Main Study Report
Abbreviations: ADM = anti-diarrhea medication; BID = twice daily; and ITT = intent-to-treat.

Other Subgroup and Geographic Analyses of ADVENT Primary Endpoint - Clinical Response

The primary endpoint was also analyzed using other subgroups to assess the robustness of the outcome and the generalizability of the primary efficacy results. For each subgroup, comparisons between Crofelemer 125 mg bid and placebo were performed using Fisher's exact test. The following subgroups were analyzed:

- Gender (Male, Female)
- Age (≤ 48 years, > 48 years)
- Race (White, Other)
- Number of watery bowel movements per day at baseline (≤ 2, > 2)
- Stool consistency score at baseline (≤ 4, > 4)
- Time since HIV diagnosis (≤ 12 years, > 12 years)
- Duration of diarrhea (≤ 2 years, > 2 years)
- HIV viral load at baseline (< 400, ≥ 400)
- CD4 cell count at baseline (< 404, ≥ 404)
- ADM use in the 4 weeks prior to Screening (Yes, No)

Figure 6 provides a summary of each of these subgroup analyses, showing the treatment difference in percentage of responders (Crofelemer 125 mg bid vs. placebo) with associated confidence intervals and p-values. A higher percentage of patients treated with Crofelemer 125 mg bid had clinical response compared with placebo in all subgroups analyzed, supporting the generalizability of the primary efficacy endpoint results.

The largest treatment differences (>10%) in favor of Crofelemer were in the following subgroups: CD4 count < 404 (16%, p = 0.0233), ADM use in prior 4 weeks (15%, p = 0.0039), HIV diagnosis > 12 years (14%, p = 0.0249), diarrhea duration > 2 years (11%, p = 0.0299), and use of protease inhibitors (11%, p = 0.0212). Results were more variable for subgroups with small numbers of subjects in the analysis (e.g., females, HIV viral load ≥ 400).

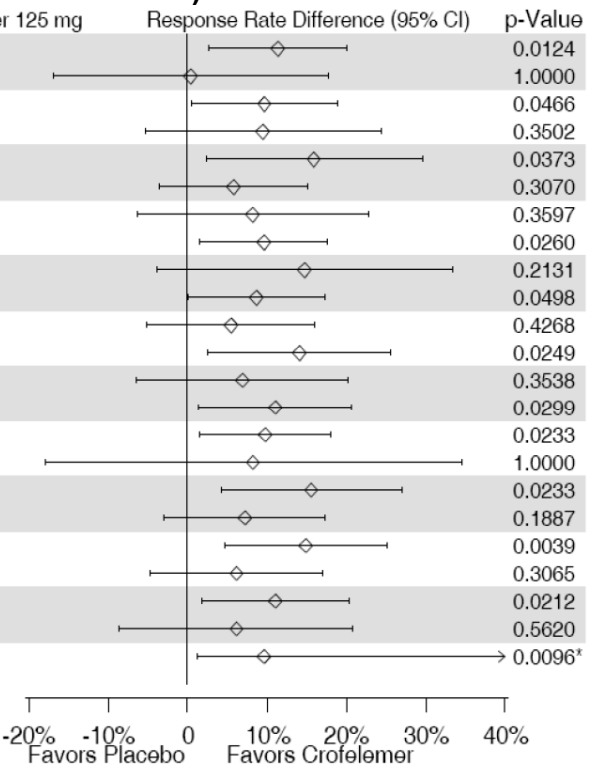
Results of the analyses suggested the following (see also Figure 6):

- Higher treatment difference in the prior ADM use subgroup than in the no prior ADM use subgroup.
- Numerically higher treatment difference in the concomitant protease inhibitor subgroup than in the no concomitant protease inhibitor subgroup.
- Numerically higher treatment difference in the CD4 cell count < 404 cells/mm^3 subgroup than in the CD4 cell count ≥ 404 cells/mm^3 subgroup.
- Similar treatment difference in the > 2 daily watery BM's subgroup than in the ≤ 2 daily watery BM's subgroup.
- Numerically higher treatment difference in the duration of diarrhea > 2 years subgroup than in the duration of diarrhea ≤ 2 years subgroup.
- Numerically higher treatment difference in the time since HIV diagnosis > 12 years subgroup than in the time since HIV diagnosis ≤ 12 years subgroup.

In summary, these results indicate that Crofelemer's efficacy was consistent across the subgroups analyzed and that the clinical responder rate was higher in patients with more severe and clinically significant diarrhea at baseline.

Figure 6: Subgroup Analyses –Primary Endpoint: Percent of Subjects with Clinical Response (Crofelemer 125 mg BID vs. Placebo)

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.

From Section 11.4.1 of the Main Study Report, Page 100
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.

Medical Officer Comments:
Although the analyses are exploratory, the results taken together support the finding that Crofelemer treatment may address the unmet medical needs of HIV/AIDS patients.

It should be noted that the results are not adjusted for multiple comparisons.

ADVENT Long-Term Efficacy – Clinical Response by Week and by Month

Table 18 summarizes clinical response by treatment group for each week in the 4-week PC phase and for each month in the 5-month PF phase. In the PC phase there was a trend of progressively higher percentages of clinical responders from week-to-week in the Crofelemer 125 mg bid and 500 mg bid treatment groups and the placebo group.

For the PF phase, the lowest percentage of responders for each treatment group was observed in Month 1 of extension treatment. The percentages of responders in each group were higher and generally consistent during Months 2, 3, 4, and 5 of Crofelemer treatment.

There was no indication of a decline in clinical response over 5 months of treatment.

Table 18: Clinical Response by Week and Month: PC Phase and PF Phase (Safety Population: Stage I + Stage II)

	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo BID n (%)
Placebo-Controlled Treatment Phase[a]				
Week 1	13/134 (10%)	5/54 (9%)	3/46 (7%)	6/137 (4%)
Week 2	18/134 (13%)	6/54 (11%)	9/44 (20%)	13/137 (9%)
Week 3	24/131 (18%)	6/54 (11%)	7/44 (16%)	13/131 (10%)
Week 4	25/127 (20%)	5/54 (9%)	14/40 (35%)	14/129 (11%)
Placebo-Free Extension Phase[b]				
Month 1	83/219 (38%)	16/67 (24%)	14/50 (28%)	
Month 2	99/209 (47%)	26/59 (44%)	17/48 (35%)	
Month 3	110/199 (55%)	25/57 (44%)	16/47 (34%)	
Month 4	102/189 (54%)	23/53 (43%)	20/44 (46%)	
Month 5	106/186 (57%)	26/52 (50%)	16/42 (38%)	

From Section 11.4.1 of the Main Study Report, Page 106
Abbreviations: BID = twice daily; PC = placebo controlled; and PF = placebo free.
a. For the PC phase, clinical response in a week was defined as ≤ 2 watery stools during a given week.
b. For the PF phase, clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of each month.

Figure 7 provides a graphical display of clinical response by week during the study, comparing subjects randomized to Crofelemer 125 mg bid (N=136) versus placebo subjects who crossed over to Crofelemer 125 mg bid treatment during the PF phase (N=99). The figure shows the percentage of subjects with clinical response at each week and provides a dividing line between the PC phase and the PF phase for reference.

In the PC phase, higher percentages of Crofelemer patients compared with placebo patients achieved clinical response at each week. In the Crofelemer group there was also a trend toward increasing numbers of responders at each consecutive week of treatment, whereas there was no notable change in the responder rate in the placebo group during Weeks 2, 3, and 4.

In the PF phase, there was a notable increase in the percentage of clinical responders of the placebo group immediately after crossover to Crofelemer 125 mg treatment. It appeared to be a persistent anti-diarrheal effect (up to 40% to 50% responders) for both

the placebo crossover patients and the patients that continued on Crofelemer. The patients who dropped out were considered non-responders.

Figure 7: Percentage of Subjects with Clinical Response by Week – ITT Population

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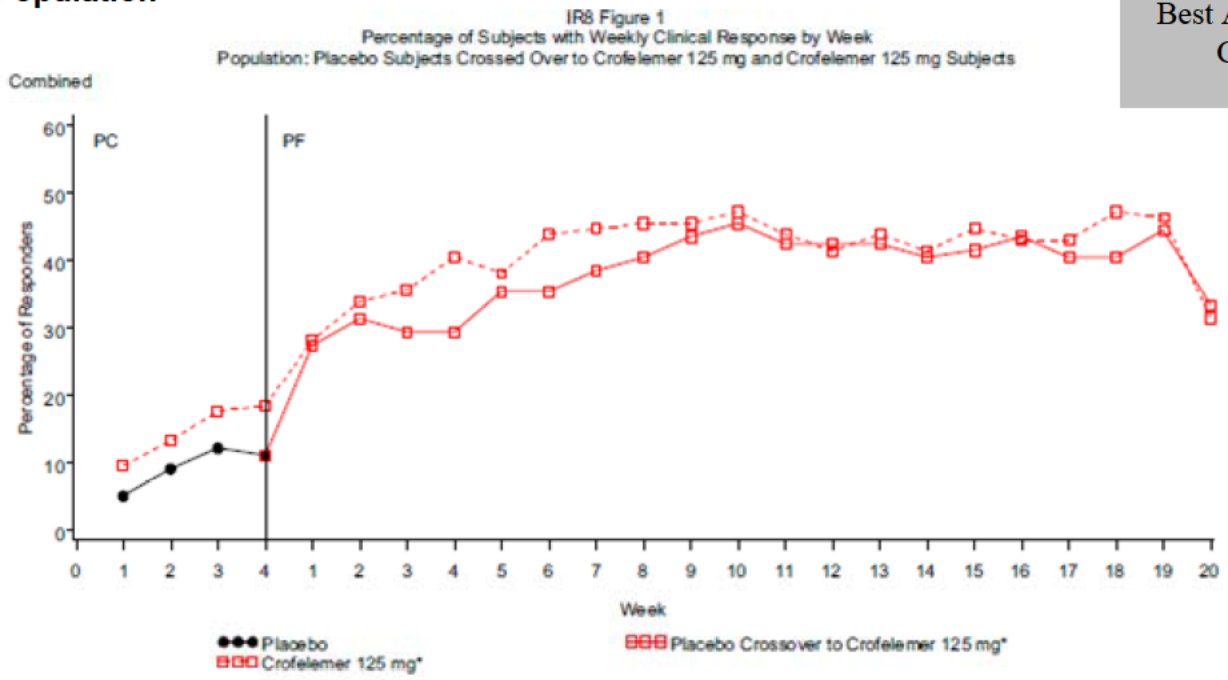


* Optimal crofelemer dose.

From Section 11.4.1 of the Main Study Report and additional information requested
Abbreviations: PC = placebo-controlled treatment phase; and PF = placebo-free extension phase.

Medical Officer Comments:
To the reviewer's knowledge, this is the first demonstration of a 20-week persistent anti-HIV diarrheal effect in this field. Both the placebo crossover patients and the patients that continued on Crofelemer appeared to be responsive. The patients who dropped out were considered non-responders.

Approximately 16% (35/220) of Crofelemer 125 mg patients dropped out during the PF phase. The most common reasons were withdrawal of consent, loss to follow-up, and noncompliance with study drug.

It should be noted that the PF phase is uncontrolled. Also, the PF phase allowed concomitant ADMs: 68% (126/185) of patients used concomitant ADMs for a mean time of 12 days during the 20-weeks study, i.e., 8% of the 20-week period.

6.1.5 Analysis of Secondary Endpoints

The changes from baseline to the end of the PC phase of the secondary endpoints are presented in Table 19. Daily watery bowel movement (p = 0.0424) and daily stool consistency score (p = 0.0166) were significantly higher in the Crofelemer 125 group versus the placebo.

Table 19: Secondary Efficacy Endpoints – Mean Change from Baseline to End of PC Phase (Crofelemer 125 mg bid vs. Placebo)

Secondary Efficacy Endpoint	Crofelemer 125 mg BID (n = 136	Placebo (n = 138)	p-value[a]
1) Number of Watery Bowel Movements / Day			0.0424
Mean Change from Baseline to Week 4 (SD)	-0.96 (1.495)	-0.75 (1.519)	
Median (Min, Max)	-0.57 (-6.1, 4.2)	-0.57 (-7.5, 3.1)	
LS Mean Difference (C – PLA) [95% CI])	-0.32 (-0.64, -0.01)		
2) Daily Stool Consistency Score			0.0166
Mean Change from Baseline to Week 4 (SD)	-0.43 (0.642)	-0.28 (0.487)	
Median (Min, Max)	-0.21 (-3.1, 0.9)	-0.17 (-2.6, 1.0)	
LS Mean Difference (C – PLA) [95% CI])	-0.16 (-0.29, -0.03)		
3) Daily Abdominal Pain/Discomfort Score			0.4136
Mean Change from Baseline to Week 4 (SD)	-0.28 (0.599)	-0.21 (0.504)	
Median (Min, Max)	-0.14 (-2.1, 1.0)	0.00 (-2.9, 1.1)	
LS Mean Difference (C – PLA) [95% CI])	-0.05 (-0.17, 0.07)		
4) Days Per Week of Urgency			0.2689
Mean Change from Baseline to Week 4 (SD)	-1.56 (2.667)	-1.26 (2.359)	
Median (Min, Max)	-1.00 (-7.0, 6.0)	-0.33 (-7.0, 6.0)	
LS Mean Difference (C – PLA) [95% CI])	-0.31 (-0.86, 0.24)		
5) Days Per Week of Fecal Incontinence			0.2149
Mean Change from Baseline to Week 4 (SD)	-1.00 (2.272)	-0.66 (2.083)	
Median (Min, Max)	0.00 (-7.0, 7.0)	0.00 (-7.0, 6.0)	
LS Mean Difference (C – PLA) [95% CI])	-0.29 (-0.76, 0.17)		
6) Number of Bowel Movements Per Day			0.3513
Mean Change from Baseline to Week 4 (SD)	-0.63 (2.402)	-0.47 (1.850)	
Median (Min, Max)	-0.43 (-17.8, 6.4)	-0.36 (-10.2, 5.9)	
LS Mean Difference (C – PLA) [95% CI])	-0.20 (-0.62, 0.22)		

From Section 11.4.1 of the Main Study Report, Page 109
Abbreviations: BID = twice daily; C = crofelemer; CI = confidence interval; LS = least square; PLA = placebo.
a. P-values were from an analysis of covariance (ANCOVA) model, including treatment effect and baseline as covariates.

Daily Watery Bowel Movements

Table 20 presents a summary of mean change from baseline to the end of Week 4 (i.e., end of the PC phase) in daily watery bowel movements for each treatment group during the PC phase (Stage 1 and Stage 2 combined).

At baseline, mean daily watery bowel movement frequency was similar in each treatment group, ranging from 2.62 to 3.04 watery stools/day. There was a statistically significant reduction in mean daily watery bowel movement frequency from baseline in the Crofelemer 125 mg bid group (LS Mean Diff: -0.32, p = 0.0424) compared with the placebo group. A statistically significant difference (data not shown) in favor of the Crofelemer 500 mg BID group versus placebo was also observed at Week 3 (LS Mean Diff: -0.52, p = 0.0237) and Week 4 (LS Mean Diff: -0.51, p = 0.0244).

Table 20: Change from Baseline to Week 4 in Daily Watery Bowel Movements (PC Phase - ITT Population)

Parameter / Statistic	Crofelemer 125 mg BID (N =136) n (%)	Crofelemer 250 mg BID (N = 54) n (%)	Crofelemer 500 mg BID (N = 46) n (%)	Placebo (N = 138) n (%)
Mean Change from Baseline to Week 4 (SD)	-0.96 (1.495)	-0.83 (1.299)	-1.11 (1.316)	-0.75 (1.519)
LS Mean Difference (95% CI)	-0.32 (-0.64, -0.01)	-0.21 (-0.63, 0.20)	-0.51 (-0.95, -0.07)	---
p-value[a]	0.0424	0.3164	0.0244	---

From Section 11.4.1 of the Main Study Report, Page 110
Abbreviations: BID = twice daily; CI = confidence interval; LS = least squares; SD = standard deviation.
Note: Baseline = average # of watery stools per day during the 7 days prior to the first dose of randomized study drug.
a. From ANCOVA, including treatment effect and baseline as a covariate in the model.

Stool Consistency Mean Change from Baseline Analysis

Table 21 presents a summary of mean change from baseline to Week 4 (end of the PC phase) of daily stool consistency score for each treatment (Stage 1 and Stage 2 combined). Stool consistency was scored for each bowel movement in the study as follows: 1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery.

Mean daily stool consistency scores were similar at baseline for each treatment group (range: 4.33 to 4.44), and consistent with loose and watery stools. There were significantly larger reductions (i.e., improvements to more formed stools) from baseline to Week 4 in stool consistency score in the Crofelemer 125 mg bid group (LS Mean Diff: -0.16, p = 0.0166) and in the Crofelemer 500 mg bid group (LS Mean Diff: -0.20, p = 0.0312) compared with placebo.

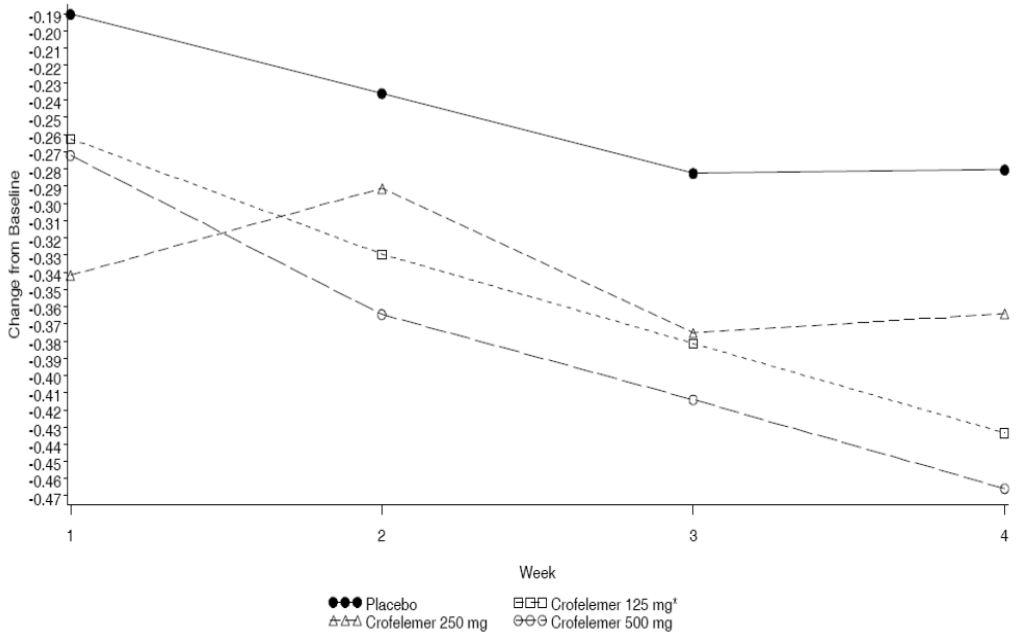
Table 21: Change from Baseline to Week 4 in Daily Stool Consistency Score (PC Phase Combined- ITT Population)

Parameter / Statistic	Crofelemer 125 mg BID (N =136) n (%)	Crofelemer 250 mg BID (N = 54) n (%)	Crofelemer 500 mg BID (N = 46) n (%)	Placebo (N = 138) n (%)
Mean Change from Baseline (SD)	-0.43 (0.642)	-0.36 (0.500)	-0.47 (0.526)	-0.28 (0.487)
LS Mean Difference (95% CI)	-0.16 (-0.29, -0.03)	-0.07 (-0.24, 0.11)	-0.20 (-0.38, -0.02)	---
p-value[a]	0.0166	0.4483	0.0312	---

From Section Section 11.4.1 of the Main Study Report, Page 111
Abbreviations: BID = twice daily; CI = confidence interval; LS = least squares; SD = standard deviation.
Note: Baseline = average daily stool consistency scores during the 7 days prior to the first dose of randomized study drug.
a. From ANCOVA, including treatment effect and baseline as a covariate in the model.

Figure 8 presents a summary of change from baseline in daily stool consistency by week and by treatment group for the PC phase. Each of the Crofelemer treatment groups had greater reductions from baseline at each week in comparison with the placebo group.

Figure 8: Change from Baseline in Stool Consistency Score by Treatment and Week (PC Phase Combined- ITT Population)



From Section 11.4.1 of the Main Study Report, Page 111

Responder Analysis

A responder analysis was performed for stool consistency, with a stool consistency responder defined as a subject with a weekly average stool consistency score < 4 for at

least 2 of the 4 weeks of the PC phase. Results of this analysis are summarized in Table 22 for each study stage and for the combined analysis of Stages 1 and 2.

In Stage 1, an increase in dose resulted in an increase in stool consistency response with statistical significance in the Crofelemer 500 mg bid group (Δ = 28%, 1-sided p = 0.0021). This dose response trend was statistically significant (p = 0.039). No statistically significant differences were observed between the Crofelemer 125 mg bid group and the placebo group in the combined responder analysis for stool consistency.

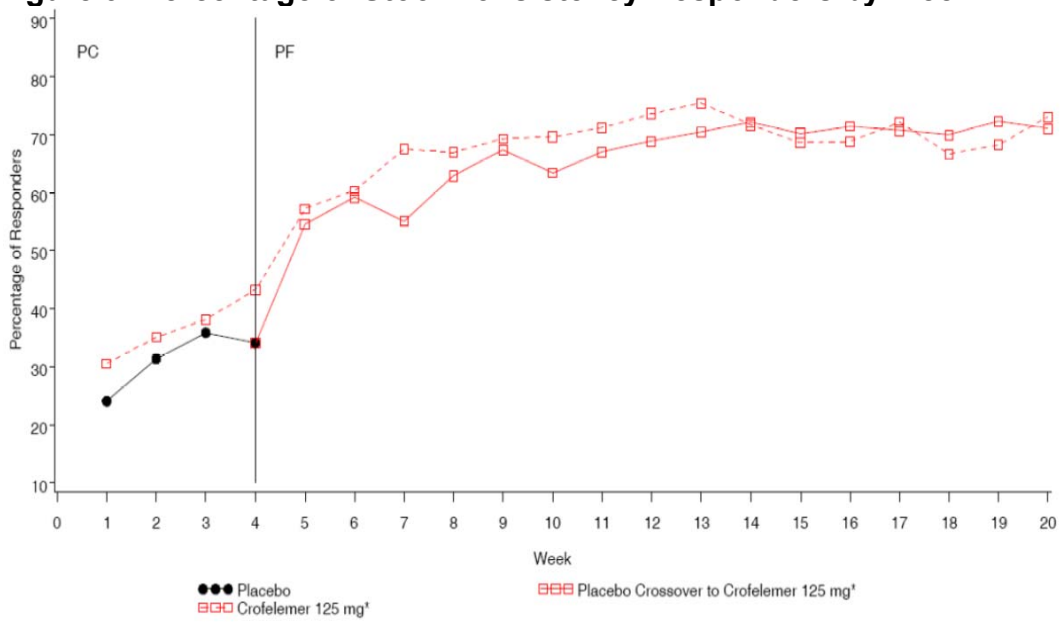
Table 22: Percentage of Subjects with Stool Consistency Response (Crofelemer vs. Placebo – Placebo-Controlled Treatment Phase (ITT Population)

Parameter/Statistic[b]	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo BID n (%)
Stage I				
Responder – n/N (%)	14/44 (31.8%)	20/54 (37.0%)	23/46 (50.0%)	11/50 (22.0%)
Treatment Difference	9.8%	15.0%	28.0%	
1-sided 97.5% CI	(-8.1%, ∞)	(-2.6%, ∞)	(8.8%, ∞)	
1-sided p-value	0.1412	0.0470	0.0021	
Stage II				
Responder – n/N (%)	39/92 (42.4%)			38/88 (43.2%)
Treatment Difference	-0.8%			
1-sided 97.5% CI	(-15.2%, ∞)			
1-sided p-value	0.4573			
Combined				
Responder – n/N (%)	53/136 (39.0%)			49/138 (35.5%)
Treatment Difference	3.5%			
1-sided 97.5% CI	(-5.0%, ∞)			
1-sided p-value	0.1428			

From Section 11.4.1 of the Main Study Report, Page 112
Abbreviations: BID = twice daily; and CI = confidence interval.
a. Stool consistency response was defined as a < 4 stool consistency score at least 2 of the 4 efficacy assessment weeks.
b. P-values and CIs were calculated based on Posch and Bauer Approach (see the statistical analysis plan for the placebo-controlled treatment phase in Appendix 16.1.9.1).

Figure 9 displays stool consistency responders by week during the study, comparing subjects randomized to Crofelemer 125 mg bid (N=136) and placebo patients who crossed over to Crofelemer 125 mg bid treatment during the PF phase (N=99). Response in a week was defined as a stool consistency score < 4 during a given week. Higher percentages of Crofelemer patients compared with placebo patients were stool consistency responders at each week during the PC phase. At Week 4, the percentage of responders was 43% in the Crofelemer 125 mg bid group versus 34% in the placebo group. Overall, although uncontrolled, there was no evidence of a decline in the Crofelemer response rate for stool consistency over 20 weeks of treatment.

Figure 9: Percentage of Stool Consistency Responders by Week



From Section 11.4.1 of the Main Study Report, Page 113
Abbreviations: PC = placebo-controlled treatment phase; and PF = placebo-free extension phase.

Daily Abdominal Pain and Discomfort Score

The daily abdominal pain or discomfort score was defined as follows: none=0, mild=1, moderate=2, severe =3. A reduction for abdominal pain score indicated improvement from baseline. At baseline, mean abdominal pain scores in the study were consistent with only mild abdominal pain and discomfort, with scores ≤ 1.03 in each treatment group. Each treatment group experienced reductions (i.e., improvements) from baseline in mean daily abdominal pain scores in the PC phase (data not shown). However, there were no statistically significant differences between the Crofelemer 125 mg bid group and the placebo group.

Days Per Week Subjects Experienced Urgency

The mean change from baseline in the number of days per week patients experienced urgency was compared with that with placebo. During the PC phase, there were no statistically significant differences between the Crofelemer and placebo groups of change from baseline in days per week with urgency (data not shown).

Days Per Week Subjects Experienced Fecal Incontinence

Mean change from baseline in the number of days per week of fecal incontinence was compared with that with placebo. The Crofelemer 125 mg bid group showed numerically larger reductions from baseline at each week in the PC phase compared with placebo (data not shown). Numeric changes in favor of Crofelemer 125 mg bid were observed versus placebo in change from baseline at Week 1 and at Week 2 (data

not shown). No statistical significance was observed in the analysis of fecal incontinence.

Number of Bowel Movements Per Day
There were no statistically significant differences observed between treatment groups and the placebo group in change from baseline in the mean daily number of bowel movements (data not shown).

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

There was no additional subpopulation in Study ADVENT.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The doses and dosing regimen of Crofelemer in Study ADVENT were chosen based on the previous clinical experience in the treatment of HIV diarrhea and other types of diarrhea. The 500 mg qid dose was used in Studies 37,554-209 and 37,554-210. The results show that Crofelemer treatment improved diarrhea symptoms. The 125 mg bid and 250 mg bid doses were used in the studies of IBS, traveler's diarrhea, and non-specific diarrhea.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy or tolerance effects was studied in Study ADVENT in a 20-week placebo-free phase (see Section 6.1.4).

6.1.10 Additional Efficacy Issues/Analyses

There was no additional efficacy issues/analyses.

7 Review of Safety

Highlights of safety findings:

- No deaths were considered drug related (HIV Integrated Safety Population, 696 patients).

- Serious Adverse Events (SAEs) were infrequent: 3% (19/696) in Crofelemer group, 2% (6/274) in Placebo (HIV integrated safety database).
    - Anemia, pneumonia, depression, and suicide attempt were the most frequent SAEs of Crofelemer groups, and each reported for 2 subjects (0.3%, 2/696).

- No discontinuations due to treatment emerged adverse events (TEAEs) during the PC phase (0% vs. 3%); Infrequent discontinuations (2%) due to AEs during the PF phase (ADVENT).

- Most frequent TEAEs occurred in Infections & Infestations (20% vs. 8%) & GI Disorder (16% vs. 9%) SOCs (Integrated 696 pts).
    - Upper respiratory tract infection (3.0% vs. 1.5%), nausea (2.6% vs. 1.5%), and back pain (2.2% vs. 1.5%) were the most frequent AEs that were numerically higher than the placebo (Integrated 696 pts)

- No ECG signals suggesting a cardiac safety risk (Integrated 696 pts)

- No evidence to suggest an effect on HIV status or ART efficacy (ADVENT)

Limitations of the available data:

There was no long-term safety study (1 year study). Enrollment in a 48-week, open-label, Phase 3 trial CFHD3092 was completed (Section 7.7). As of the data cut-off of December 31, 2011 for the 120-day update, 251 subjects were enrolled, 250 subjects received Crofelemer, and 218 subjects are currently ongoing. No deaths have been reported in CFHD3092, 12 subjects (5%) experienced treatment-emergent SAEs (none were considered related to study medication), and 8 subjects (3%) had TEAEs resulting in discontinuation of trial drug.

The current evaluation was based on Study ADVENT, a two-stage study (362 patients) with 4-week placebo-controlled phase and 20-week placebo-free phase. Two supportive placebo-controlled studies [Study 37554-209 (4-day Crofelemer treatment in 43 patients) and Study 37554-210 (7-day Crofelemer treatment in 302 patients)] were also reviewed.

7.1 Methods

The primary safety review was based on a Phase 3 trial (ADVENT) both alone and integrated with data from 2 additional trials (37554-210, and 37554-209) in 696 patients with HIV diarrhea. Table 23 provides an overview of the studies in the primary integrated analysis.

Table 23: Overview of Primary Analysis Studies for Crofelemer for Diarrhea in HIV+ Individuals

Category	ADVENT	37554-210	37554-209
Study Design	Randomized, double-blind, placebo-controlled, multicenter	Randomized, double-blind, placebo-controlled, multicenter	Randomized, double-blind, placebo-controlled, multicenter (2 sites)
Subject Population	Males and females, aged ≥ 18 years, with HIV-1 infection, and a history of diarrhea for ≥ 1 month	Males and females, aged ≥ 18 years, with HIV-1 infection, and a history of diarrhea for ≥ 14 days	Males and females, 18-60 years, with HIV infection and met CDC criteria for AIDS, and had abnormal stool weight > 200 g and ≥ 3 abnormal stools during 24-hour Screening period
Treatment Groups	Crofelemer: 125 mg tablet, 250 mg tablet, or 2×250 mg tablet (500 mg) BID Placebo: BID	Crofelemer: 250 mg tablet, 500 mg tablet, or 500 mg beads QID Placebo: QID	Crofelemer: 2×250 mg beads (500 mg) in capsule QID Placebo: QID
Treatment Duration	Crofelemer: 4-week placebo-controlled phase and 20-week placebo-free phase (so 20 or 24 weeks) Placebo: 4 weeks	Crofelemer 250 mg tablet and 500 mg tablet and placebo: 6-day inpatient period + 21-day outpatient period Crofelemer 500 mg beads: 6-day inpatient period, then switched to 500 mg tablets for 21-day outpatient period	4 days
Follow-up Duration	14 days	7 days	7-9 days
Scheduled Visit During Treatment	Days -4, 14, 29, 57, 87, 113, 141, 169, 183 (phone)	Days 1-7 inpatient, Day 14, Day 21, Day 28, Day 35	Days 1-4 inpatient, follow up 7-9 days after discharge
Countries	United States, Puerto Rico	United States	United States
Number of Subjects	376 total subjects (362 crofelemer, 138 placebo) [a] at 70 centers	400 total subjects (302 crofelemer, 98 placebo) at 25 centers	85 total subjects (43 crofelemer, 42 placebo) at 2 centers

From Studies ADVENT, 37554-210, 37554-209.
Abbreviations: BID = twice daily; CDC = Centers for Disease Control; HIV = human immunodeficiency virus; QID = 4 times daily.

For the primary integrated safety analyses, 3 pools were used, and were defined as follows:

- PC Phase Safety Population in ADVENT: including subjects who received at least 1 dose of trial drug and had at least 1 post-baseline safety assessment in the placebo-controlled phase of the ADVENT trial. This information was taken directly from the tables and listings for the ADVENT Clinical Study Report (placebo or Crofelemer experience during placebo-controlled phase of ADVENT).

- Long-Term Crofelemer Experience Safety Population in ADVENT: including subjects who received at least 1 dose of Crofelemer and had at least 1 post-baseline safety assessment in the ADVENT trial (Crofelemer experience during placebo-controlled and placebo-free phases of ADVENT).

- HIV Integrated Safety Population (Diarrhea in HIV+ Individuals): including subjects who received at least 1 dose of trial drug and had at least 1 post-baseline safety assessment in any of the 3 Crofelemer trials for treatment of diarrhea in HIV+ individuals [placebo or Crofelemer groups during ADVENT (placebo-controlled and placebo-free phases), 37554-210, and 37554-209].

The safety evaluation includes vital signs, physical examination, concomitant medications, blood chemistry, hematology (coagulation), CD4 and CD8 counts, HIV titer, urinalysis, stool test, ECG, and PRO assessments findings, and adverse events. AE collection methods included review of staff documentation, physical exams of patients, PRO assessments, and review of procedural test information. The AE safety nomenclature for this study was MedDRA.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation included two Phase 3 clinical trials (Studies ADVENT and 37554-210) and one Phase 2 trial (Study 37554-209) in adult patients with HIV associated diarrhea.

7.1.2 Categorization of Adverse Events

The adverse events were correctly coded based on MedDRA.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

7.1.3.1 Incidence of AEs at ADVENT PC Phase

In the PC phase, the incidence of all TEAEs (all Crofelemer 27%, placebo 33%), severe TEAEs (1%, 4%), TEAEs leading to trial drug discontinuation (0%, 3%), and SAEs (1%, 3%) were higher in the placebo group compared with the all Crofelemer subjects group (Table 24, combined analysis of Stages 1 and 2). The percentage of patients with TEAEs during PC treatment was similar in the Crofelemer 125 mg bid group compared with placebo (35% vs. 33%). The incidence of drug-related TEAEs was numerically higher in the all Crofelemer group compared with the placebo group (all Crofelemer 6%, placebo 4%), although the rates were comparable or lower when adjusted for exposure duration (i.e., person years of exposure, PEY): Crofelemer 21.3 PEY, placebo 12.1 PEY.

Table 24: Summary of Adverse Events (ADVENT PC Phase, Stages 1 and 2 Combined)

Subjects with TEAEs	Crofelemer 125 mg BID N = 130 n (%)	Crofelemer 250 mg BID N = 54 n (%)	Crofelemer 500 mg BID N = 42 n (%)	All Crofelemer N = 226 n (%)	Placebo BID N = 137 n (%)
Any TEAEs	45 (34.6)	10 (18.5)	7 (16.7)	62 (27.4)	45 (32.8)
Severe[a]	2 (1.5)	1 (1.9)	0	3 (1.3)	5 (3.6)
Moderate	16 (12.3)	6 (11.1)	2 (4.8)	24 (10.6)	16 (11.7)
Mild	27 (20.8)	3 (5.6)	5 (11.9)	35 (15.5)	24 (17.5)
Drug-related TEAEs	9 (6.9)	2 (3.7)	2 (4.8)	13 (5.8)	5 (3.6)
SAEs	2 (1.5)	0	0	2 (0.9)	4 (2.9)
TEAEs Leading to Discontinuation	0	0	0	0	4 (2.9)
Deaths	0	0	0	0	1 (0.7)

From Section 2.7.4, Summary of Clinical Safety, Page 55
Abbreviations: BID = twice daily; CSR = clinical study report; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a. If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity.

7.1.3.2 Incidence of AEs at ADVENT Long-Term Phase

Exposure to Crofelemer during the long-term phase was over 6 times longer than the Crofelemer PC phase (125 mg bid 88.7 PEY vs. 12.1 PEY; all Crofelemer 136.5 PEY vs. 21.3 PEY). After adjustment for exposure duration, the incidence of any TEAEs, SAEs, drug-related TEAEs, severe TEAEs, and TEAEs leading to trial drug discontinuation was comparable to or lower in the long-term population compared with the PC phase population (Table 25).

Table 25: Summary of Adverse Events (Long-Term Crofelemer Experience Safety Population – ADVENT)

Subjects with TEAEs	Crofelemer 125 mg BID N = 229 n (%)	Crofelemer >125 mg BID N = 123 n (%)	All Crofelemer N = 352 n (%)
Any TEAEs	145 (63.3)	67 (54.5)	212 (60.2)
Severe[a]	13 (5.7)	5 (4.1)	18 (5.1)
Moderate	69 (30.1)	30 (24.4)	99 (28.1)
Mild	63 (27.5)	32 (26.0)	95 (27.0)
Drug-related TEAEs	27 (11.8)	11 (8.9)	38 (10.8)
SAEs	11 (4.8)	4 (3.3)	15 (4.3)
TEAEs Leading to Discontinuation[b]	5 (2.2)	1 (0.8)	6 (1.7)
Deaths	1 (0.4)	0	1 (0.3)

From Section 2.7.4 Summary of Clinical Safety, Page 56
Abbreviations: BID = twice daily; LTCE = long-term Crofelemer experience; SAE = serious adverse event; TEAE = treatment emergent adverse event.
a. If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity.
b. The number of subjects listed as discontinuing as a result of an AE in this in-text table differs from the source table and listing. For Subject HV101-0011-0053 in the Crofelemer 125 mg group, a TEAE of "pain in extremity" was mistakenly recorded as a TEAE leading to trial drug discontinuation in the subject case report form. This subject continued on trial drug after onset of the TEAE of "pain in extremity" and did not discontinue prematurely from the trial.

7.1.3.3 Incidence of AEs in HIV Integrated Safety Population

The incidence of TEAEs in the HIV Integrated Safety population (ADVENT, 37554-210, and 37554-209 trials) was numerically higher in the Crofelemer groups (250 mg daily = 63%, > 250 mg daily = 51%, and all Crofelemer = 55%) than in the placebo group (37%) in the HIV+ Integrated Safety population (Table 26). When normalized for exposure duration (Crofelemer 250 mg daily = 88.7 PEY, Crofelemer > 250 mg daily = 60.9 PEY, all Crofelemer = 149.4 PEY, placebo 16.6 PEY), the incidence of TEAEs was lower in the Crofelemer groups than in the placebo group. The incidence of drug-related AEs was higher in the >250 mg daily Crofelemer group compared to the 250 mg daily group. Drug-related TEAEs, TEAEs leading to discontinuation of trial drug, and deaths were reported for similar proportions of subjects in the Crofelemer 250 mg daily and placebo groups. Serious AE rates were low (≤ 5%) in all groups.

Table 26: Overall Summary of Adverse Events (HIV Integrated Safety Population)

Subjects with TEAEs	Crofelemer 250 mg Daily N = 229 n (%)	Crofelemer >250 mg Daily N = 467 n (%)	All Crofelemer N = 696 n (%)	Placebo N = 274 n (%)
Any TEAEs	145 (63.3)	238 (51.0)	383 (55.0)	100 (36.5)
Severe[a]	13 (5.7)	16 (3.4)	29 (4.2)	10 (3.6)
Moderate	69 (30.1)	80 (17.1)	149 (21.4)	34 (12.4)
Mild	63 (27.5)	142 (30.4)	205 (29.5)	56 (20.4)
Drug-related TEAEs	27 (11.1)	107 (22.9)	134 (19.3)	34 (12.4)
SAEs	11 (4.8)	8 (1.7)	19 (2.7)	6 (2.2)
TEAEs Leading to Discontinuation[b]	5 (2.2)	10 (2.1)	15 (2.2)	7 (2.6)
Deaths	1 (0.4)	0	1 (0.1)	1 (0.4)

From Section 2.7.4 Summary of Clinical Safety, Page 57
Abbreviations: HIV+ = human immunodeficiency virus positive; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a. If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity.
b. The number of subjects listed as discontinuing as a result of an AE in this in-text table differs from the source table and listing. For Subject HV101-0011-0053 in the Crofelemer 125 mg group, a TEAE of "pain in extremity" was mistakenly recorded as a TEAE leading to trial drug discontinuation in the subject case report form. This subject continued on trial drug after onset of the TEAE of "pain in extremity" and did not discontinue prematurely from the trial.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Crofelemer has been studied in approximately 1,800 subjects in controlled clinical trials in healthy subjects, and patients with diarrhea or viral respiratory diseases:

- Healthy subjects (70 subjects);
- Diarrhea patients with one of the following conditions (1,699 patients):
  - Diarrhea in HIV positive individuals, d-IBS, travelers' diarrhea, non-specific diarrhea, or acute infectious diarrhea using enteric coated beads or tablets.
- Viral respiratory diseases (b) (4)

For the primary integrated safety analyses of HIV diarrhea, 3 pools were used, and were defined as follows:

- PC Phase Safety Population in ADVENT: including subjects who received at least 1 dose of trial drug and had at least 1 post-baseline safety assessment in the placebo-controlled phase of the ADVENT trial.

- Long-Term Crofelemer Experience Safety Population in ADVENT: including subjects who received at least 1 dose of Crofelemer and had at least 1 post-baseline safety assessment in the ADVENT trial (placebo-controlled and placebo-free phases of ADVENT).

- HIV Positive Integrated Safety Population (Diarrhea in HIV+ Individuals): including subjects who received at least 1 dose of trial drug and had at least 1 post-baseline safety assessment in any of the 3 Crofelemer trials for treatment of diarrhea in HIV+ individuals (ADVENT, 37554-210, and 37554-209 trials).

7.2.1.1 Drug exposure

The HIV positive integrated safety population (ADVENT, 37554-210, and 37554-209 trials) included 229 patients who received Crofelemer 250 mg daily for a mean of 141 days and 467 patients who received Crofelemer > 250 mg daily for a mean of 48 days (Table 27). Of patients who received Crofelemer 250 mg daily, 94 patients (41%) took the drug for 3 to 6 months and 101 patients (44%) took the drug for 6 to 12 months.

Table 27: summary of Trial Drug Exposure (HIV Integrated Safety Population)

Duration (days)	Crofelemer 250 mg Daily N = 229	Crofelemer >250 mg Daily N = 467	Total Crofelemer N = 696	Placebo N = 274
Mean (SD)	141.4 (43.99)	47.6 (62.32)	78.5 (72.0)	22.1 (12.81)
Median (min, max)	147.0 (12, 185)	27.0 (1, 227)	29.0 (1, 227)	28.0 (2, 42)

From Table 10, Section 2.7.4 Summary of Clinical Safety; max: maximum; min: minimum; SD: standard deviation, Page 46

For the 4-week ADVENT PC phase, the mean exposure duration was 33 days (N = 236) (Table 28)

Table 28: Summary of Study Drug Exposure (ADVENT Safety Population)

Population	Crofelemer 125 mg BID	Crofelemer 250 mg BID	Crofelemer 500 mg BID	Total Crofelemer	Placebo BID
Placebo-Controlled Treatment Phase					
Exposure Duration (Days)					
N	**136**	**54**	**46**	**236**	**138**
Mean (SD)	32.9 (4.62)	33.9 (1.96)	31.8 (5.47)	32.9 (4.39)	32.1 (5.56)
Median (Min, Max)	33.5 (1, 45)	34.0 (30,39)	33.0 (6, 37)	34.0 (1, 45)	33.0 (1, 42)
Placebo-Free Extension Phase					
Exposure Duration (Days)					
N	**220**	**67**	**50**	**337**	
Mean (SD)	127.6 (35.22)	115.9 (45.50)	129.6 (32.21)	125.5 (37.29)	
Median (Min, Max)	140.0 (2, 151)	139.0 (1, 148)	139.5 (17, 197)	140.0 (1, 197)	

From Section 12.1, ADVENT Main Study Report, Pages 124
Abbreviations: BID = twice daily; and SD = standard deviation.

Overall compliance in the ADVENT PC phase was > 90%, based on the number of tablets dispensed, returned, and days of exposure for each treatment group (Table 31; Stages 1 and 2 combined). Most patients in each treatment group (range: 87% to 98%) received ≥ 80% of the scheduled treatment doses. Subject compliance was also high (> 95%) in each of the Crofelemer treatment groups during the PF phase of the trial and most Crofelemer-treated patients (320/337, 95%) received ≥ 80% of the scheduled treatment doses.

Table 29: Summary of Trial Drug Compliance (ADVENT PC Phase Safety Population, Stages I and II Combined)

Parameter	Crofelemer 125 mg BID N = 136	Crofelemer 250 mg BID N = 54	Crofelemer 500 mg BID N = 46	All Crofelemer N = 236	Placebo BID N = 138
Calculated Compliance[a]					
Mean (SD)	96.5 (14.1)	97.3 (6.0)	91.8 (15.2)	95.8 (13.1)	96.8 (10.3)
Compliance Category n (%)					
≥ 80% Compliance	125 (91.9)	53 (98.1)	40 (87.0)	218 (92.4)	129 (93.5)
< 80% Compliance	11 (8.1)	1 (1.9)	6 (13.0)	18 (7.6)	7 (5.1)
Missing	0	0	0	0	2 (1.4)

From Section 2.7.4, Summary of Clinical Safety, Page 46
Abbreviations: BID = twice daily; SD = standard deviation SD = standard deviation.
a. Compliance was calculated as: [(total # dispensed – total # returned) / (exposure duration in days x 4)] x 100.

Exposure durations (i.e., person years of exposure, PEY) were calculated for each phase as the sum of exposure days for all treated subjects (mean exposure × number of subjects) included in the analysis divided by 365.25; these are provided in Table 30.

Table 30: Summary of Exposure Durations (PEY) in HIV Populations

Population	Crofelemer							Placebo
	125mg BID	>125mg BID	250mg BID	500mg BID	250mg Daily	>250mg Daily	All	
ADVENT PC Phase	12.1		5.0	4.0			21.3	12.1
Long-Term Crofelemer	88.7	47.8					136.5	
HIV+ Integrated					88.7	60.9	149.4	16.6

From Section 2.7.4, Summary of Clinical Safety, Page 47
Abbreviations: BID = twice daily; HIV+ = human immunodeficiency virus positive, PEY = person exposure years; PC = placebo controlled; TEAE = treatment-emergent adverse event.
Note: Person years of exposure were calculated for each phase as the sum of exposure days for all treated subjects (mean exposure × number of subjects) included in the analysis divided by 365.25.

Exposure duration in the ADVENT PC phase was 21.3 PEY for all Crofelemer patients (N=236), and 12.1 PEY for placebo patients (N=138). Exposure duration in the Long-Term Crofelemer Experience Safety population was 136.5 PEY for all Crofelemer subjects (N=352), 47.8 PEY for crofelemer > 125 mg bid patients (N=123), and 88.7 PEY for Crofelemer 125 mg bid patients (N=229). Exposure duration in the HIV Integrated Safety population was 149.4 PEY for all Crofelemer patients (N=696), and 16.6 PEY for placebo subjects (N=274).

Drug Exposure During ADVENT PC Phase

Mean exposure duration for the 4-week ADVENT PC phase was 33 days among all Crofelemer treated subjects (N = 236) and 32 days for placebo-treated subjects (N = 138) (Table 31, combined analysis of Stages 1 and 2).

Table 31: Summary of Trial Drug Exposure (ADVENT PC Phase Safety Population, Stages 1 and 2 Combined)

Exposure Duration (Days)	Crofelemer 125 mg BID N = 136	Crofelemer 250 mg BID N = 54	Crofelemer 500 mg BID N = 46	All Crofelemer N = 236	Placebo BID N = 138
Mean (SD)	32.9 (4.62)	33.9 (1.96)	31.8 (5.47)	32.9 (4.39)	32.1 (5.56)
Median (min, max)	33.5 (1, 45)	34.0 (30,39)	33.0 (6, 37)	34.0 (1, 45)	33.0 (1, 42)

From Section 2.7.4, Summary of Clinical Safety, Page 45
Abbreviations: BID = twice daily; CSR = clinical study report; min = minimum; max = maximum; PC = placebo-controlled; SD = standard deviation.

Overall compliance in the ADVENT PC phase, based on the number of tablets dispensed, returned, and days of exposure, was > 90% for each treatment group (Table 34; Stages 1 and 2 combined). Most subjects in each treatment group (range: 87% to 98%) received ≥ 80% of the scheduled treatment doses. Subject compliance was also high (> 95%) in each of the Crofelemer treatment groups during the PF phase of the trial and most Crofelemer-treated subjects (320/337, 95%) received ≥ 80% of the scheduled treatment doses.

Table 32: Summary of Trial Drug Compliance (ADVENT PC Phase Safety Population, Stages 1 and 2 Combined)

Parameter	Crofelemer 125 mg BID N = 136	Crofelemer 250 mg BID N = 54	Crofelemer 500 mg BID N = 46	All Crofelemer N = 236	Placebo BID N = 138
Calculated Compliance[a]					
Mean (SD)	96.5 (14.1)	97.3 (6.0)	91.8 (15.2)	95.8 (13.1)	96.8 (10.3)
Compliance Category n (%)					
≥ 80% Compliance	125 (91.9)	53 (98.1)	40 (87.0)	218 (92.4)	129 (93.5)
< 80% Compliance	11 (8.1)	1 (1.9)	6 (13.0)	18 (7.6)	7 (5.1)
Missing	0	0	0	0	2 (1.4)

From Section 2.7.4, Summary of Clinical Safety, Page 46
Abbreviations: BID = twice daily; SD = standard deviation SD = standard deviation.
a. Compliance was calculated as: [(total # dispensed – total # returned) ÷ (exposure duration in days x 4)] x 100.

Drug Exposure during Long-Term Crofelemer Experience - ADVENT

A total of 352 subjects in the Long-Term Crofelemer Experience Safety population were exposed to Crofelemer 125 mg bid (N = 229) and > 125 mg BID (N = 123) for means of 141 and 142 days, respectively, and medians of 147 and 171 days, respectively (Table 33). A total of 101 subjects were treated with Crofelemer 125 mg bid for at least 6 months and 71 subjects were treated with Crofelemer > 125 mg bid for at least 6 months.

Table 33: Summary of Trial Drug Exposure (Long-Term Crofelemer Experience Safety Population - ADVENT)

Duration (days)	Crofelemer 125 mg BID N = 229	Crofelemer > 125 mg BID N = 123	All Crofelemer N = 352
Mean (SD)	141.4 (43.99)	141.9 (48.81)	141.6 (45.66)
Median (min, max)	147.0 (12, 185)	171.0 (24, 227)	161.5 (12, 227)

From Section 2.7, Summary of Clinical Safety, Page 46
Abbreviations: LTCE = long-term crofelemer experience; max = maximum; min = minimum; SD = standard deviation.

Drug Exposure of HIV+ Integrated Safety Population

The HIV+ Integrated Safety population (ADVENT, 37554-210, and 37554-209 trials) included 229 subjects who received Crofelemer 250 mg daily for a mean of 141 days and 467 subjects who received Crofelemer > 250 mg daily for a mean of 48 days (Table 34). Of subjects who received Crofelemer 250 mg daily, 94 subjects (41%) took the drug for 3 to 6 months and 101 subjects (44%) took the drug for 6 to 12 months.

Table 34: Summary of Trial Drug Exposure (HIV+ Integrated Safety Population)

Duration (days)	Crofelemer 250 mg Daily N = 229	Crofelemer >250 mg Daily N = 467	Total Crofelemer N = 696	Placebo N = 274
Mean (SD)	141.4 (43.99)	47.6 (62.32)	78.5 (72.0)	22.1 (12.81)
Median (min, max)	147.0 (12, 185)	27.0 (1, 227)	29.0 (1, 227)	28.0 (2, 42)

From Section 2.7, Summary of Clinical Safety, Page 47
Abbreviations: HIV+ = human immunodeficiency virus positive; max = maximum; min = minimum; SD = standard deviation.

Exposure Durations Summary – Primary Analyses

Exposure durations (i.e., person years of exposure, PEY) were calculated for each phase as the sum of exposure days for all treated subjects (mean exposure x number of subjects) included in the analysis divided by 365.25; these are provided in Table 35.

Table 35: Exposure Durations (PEY) in HIV+ Populations by Dose Group

Population	Crofelemer 125mg BID	Crofelemer >125mg BID	Crofelemer 250mg BID	Crofelemer 500mg BID	Crofelemer 250mg Daily	Crofelemer >250mg Daily	Crofelemer All	Placebo
ADVENT PC Phase	12.1		5.0	4.0			21.3	12.1
Long-Term Crofelemer	88.7	47.8					136.5	
HIV+ Integrated					88.7	60.9	149.4	16.6

From ADVENT CSR Table 14.1.10, LTCE Table 1.7, HIV+ Table 1.7., Page 47
Abbreviations: BID = twice daily; HIV+ = human immunodeficiency virus positive, PEY = person exposure years; PC = placebo controlled; TEAE = treatment-emergent adverse event.
Note: Person years of exposure were calculated for each phase as the sum of exposure days for all treated subjects (mean exposure x number of subjects) included in the analysis divided by 365.25.

Exposure duration in the ADVENT PC phase was 21.3 PEY for all Crofelemer subjects (N=236), 12.3 PEY for Crofelemer 125 mg bid subjects (N=136), 5.0 PEY for Crofelemer 250 mg bid subjects (N=54), 4.0 PEY for Crofelemer 500 mg bid subjects (N=46), and 12.1 PEY for placebo subjects (N=138). Exposure duration in the Long-Term Crofelemer Experience Safety population was 136.5 PEY for all Crofelemer subjects (N=352), 47.8 PEY for crofelemer > 125 mg bid subjects (N=123), and 88.7 PEY for Crofelemer 125 mg bid subjects (N=229). Exposure duration in the HIV+ Integrated Safety population was 149.4 PEY for all Crofelemer subjects (N=696), 88.7 PEY for Crofelemer 250 mg daily subjects (N=229), 60.9 PEY for Crofelemer 250 mg daily subjects (N=467), and 16.6 PEY for placebo subjects (N=274).

7.2.1.2 Demographic and Other Characteristics of Study Population

The Crofelemer and placebo treatment groups in the HIV+ Safety population were comparable with respect to demographic and baseline characteristics, medical history, and concomitant medication use.

Demography of ADVENT PC Phase

Demographic characteristics were similar between treatment groups in the PC phase of the ADVENT trial (Table 36, combined analysis of Stages 1 and 2). Most subjects (≥ 84%) in each treatment group were male. Mean and median ages in the Crofelemer groups and the placebo group were 44 to 47 years, and all but 2 subjects in the trial were < 65 years old. White and Black subjects, as well as subjects of Hispanic ethnicity, were well represented in each treatment group; however, the Crofelemer 250 mg and 500 mg groups had higher percentages of White subjects and lower percentages of Black subjects compared with the Crofelemer 125 mg group and the placebo group.

Table 36: Demographics (ADVENT PC Phase Safety Population, Stages 1 and 2 Combined)

Characteristic/ Statistic	Crofelemer 125 mg BID N = 136	Crofelemer 250 mg BID N = 54	Crofelemer 500 mg BID N = 46	Placebo BID N = 138
Age (years)				
Mean (SD)	45.0 (7.80)	43.8 (8.37)	46.7 (8.60)	44.8 (8.45)
Median (min, max)	45.0 (23, 61)	43.5 (24, 59)	46.0 (30, 68)	46.0 (21, 63)
Sex – n (%)				
Male	110 (84.6)	48 (88.9)	36 (85.7)	115 (83.9)
Female	20 (15.4)	6 (11.1)	6 (14.3)	22 (16.1)
Race – n (%)				
White/Caucasian	51 (39.2)	34 (63.0)	24 (57.1)	58 (42.3)
Black/African American	48 (36.9)	9 (16.7)	7 (16.7)	53 (38.7)
American Indian	1 (0.8)	1 (1.9)	0	0
Other[a]	30 (23.1)	10 (18.5)	11 (26.2)	26 (19.0)
Ethnicity – n (%)				
Hispanic or Latino	30 (23.1)	10 (18.5)	11 (26.2)	24 (17.5)

From Section 2.7.4, Summary of Clinical Safety, Page 49
Abbreviations: BID = twice daily; CRF = case report form; CSR = clinical study report; max = maximum; min = minimum; SD = standard deviation.
a. "Other" includes CRF categories Asian/Pacific Islander, Hispanic, and other races. In the ADVENT trial, "Hispanic" was listed as a selectable option for race. In the post-text and in-text demographic tables, subjects recorded as "Hispanic" 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."

In the ADVENT PC Phase Safety population, the mean time since the first diagnosis of HIV was 12 to 13 years in all groups and the mean time since diarrhea had started ranged between 6 and 7 years in each treatment group (Table 37, combined analysis of Stages 1 and 2). Mean (± standard deviation, SD) CD4 cell count was 482.0/μL (243.84) and 525.7/μL (239.08) in all Crofelemer subjects and placebo subjects, respectively. Most subjects (≥ 81%) in each treatment group had no HIV ribonucleic acid (RNA) detected at baseline. A high viral load (> 1000 HIV copies/mL) was recorded in 6% of all crofelemer subjects and 7% of placebo subjects. At least 96% of subjects in

each group were using ART, and 64% to 76% of subjects in each group were using protease inhibitors.

The primary causes of diarrhea in all Crofelemer- and placebo-treated subjects were ART (72% and 75%, respectively) and HIV infection (26% and 24%, respectively) assessed by the investigators. Baseline averages for daily bowel movements (watery, loose, and total) during the 7 days prior to the first dose of trial drug were comparable between treatment groups.

In Table 37 and Table 38, categories of CD4 counts of < 404 cells/μL versus ≥ 404 cells/μL are presented. A CD4 count of 200 cells/μL is clinically meaningful in HIV+ individuals (Call, 2000). However, the number of subjects with CD4 count < 200 cells/μL at baseline in the ADVENT trial was too small to draw clinically meaningful conclusions. Therefore, subgroups and the CD4 categories shown in baseline characteristics tables (Tables 38 and 39) were based on the lower limit of normal (LLN) of 404 cells/μL for CD4 cell count (< 404 cells/μL versus ≥ 404 cells/μL).

Table 37: Baseline Diarrhea Characteristics (ADVENT PC Phase Safety Population, Stages 1 and 2 Combined)

Characteristic/ Statistic	Crofelemer 125 mg BID N = 130	Crofelemer 250 mg BID N = 54	Crofelemer 500 mg BID N = 42	All Crofelemer N = 226	Placebo BID N = 137
Time Since First Diagnosis of HIV (Years)					
Mean (± SD)	12.4 (6.32)	13.1 (6.71)	13.5 (5.73)	12.8 (6.30)	12.4 (7.53)
Median (Min, Max)	11.7 (0.3, 29.3)	13.3 (1.3, 24.0)	13.5 (3.4, 24.7)	12.6 (0.3, 29.3)	12.5 (0.3, 29.8)
CD4 Cell Count (cells/µL)					
Mean (± SD)	501.5 (235.53)	425.2 (226.13)	495.0 (282.90)	482.0 (243.84)	525.7 (239.08)
Median (Min, Max)	481.0 (111, 1183)	374.0 (100, 1095)	442.5 (149, 1734)	431.5 (100, 1734)	512.0 (76, 1298)
CD4 Cell Category, n (%)					
<404	53 (40.8)	29 (53.7)	18 (42.9)	100 (44.2)	39 (28.5)
≥404	77 (59.2)	25 (46.3)	24 (57.1)	126 (55.8)	98 (71.5)
HIV-1 Viral Load (copies/mL), n (%)					
<400 No RNA Detected	108 (83.1)	44 (81.5)	35 (83.3)	187 (82.7)	115 (83.9)
<400 RNA Detected	10 (7.7)	4 (7.4)	4 (9.5)	18 (8.0)	10 (7.3)
400 – 9999	6 (4.6)	0	1 (2.4)	7 (3.1)	3 (2.2)
≥1000	6 (4.6)	6 (11.1)	2 (4.8)	14 (6.2)	9 (6.6)
Use of Antiretroviral Therapy, n (%)					
Yes	129 (99.2)	52 (96.3)	42 (100.0)	223 (98.7)	133 (97.1)
Use of Protease Inhibitors, n (%)					
Yes	83 (63.8)	41 (75.9)	32 (76.2)	156 (69.0)	96 (70.1)
Time Since Diarrhea Started (Years)					
Mean (± SD)	6.1 (5.82)	5.5 (4.89)	7.2 (5.84)	6.1 (5.62)	6.5 (6.52)
Median (Min, Max)	4.1 (0.1, 24.5)	5.1 (0.2, 20.9)	6.3 (0.3, 22.2)	4.8 (0.1, 24.5)	4.1 (0.1, 32.4)
Cause of Diarrhea, n (%)					
Antiretroviral Therapy	97 (74.6)	37 (68.5)	28 (66.7)	162 (71.7)	103 (75.2)
HIV infection of intestine	31 (23.8)	15 (27.8)	13 (31.0)	59 (26.1)	33 (24.1)
Other	2 (1.5)	2 (3.7)	1 (2.4)	5 (2.2)	1 (0.7)

Continued

Characteristic/ Statistic	Crofelemer 125 mg BID N = 130	Crofelemer 250 mg BID N = 54	Crofelemer 500 mg BID N = 42	All Crofelemer N = 226	Placebo BID N = 137
Daily Watery Bowel Movements[a]					
Mean (± SD)	2.7 (1.67)	2.7 (1.47)	2.6 (1.06)	2.7 (1.53)	3.1 (2.09)
Median (Min, Max)	2.3 (0.7, 7.9)	2.2 (0.9, 8.0)	2.4 (0.7, 5.4)	2.4 (0.7, 8.0)	2.6 (0.9, 15.3)
Daily Loose Bowel Movements[a]					
Mean (± SD)	1.8 (1.35)	1.6 (0.82)	1.8 (1.16)	1.7 (1.21)	1.8 (1.15)
Median (Min, Max)	1.7 (0.0, 7.7)	1.6 (0.0, 4.0)	1.6 (0.0, 5.4)	1.7 (0.0, 7.7)	1.7 (0.0, 6.2)

From Section 2.7.4, Summary of Clinical Safety, Page 50
Abbreviations: BID = twice daily; CSR = clinical study report; HIV = human immunodeficiency virus; min = minimum; max = maximum; PC = placebo-controlled; RNA = ribonucleic acid; SD = standard deviation.
a. Baseline was the average of daily data from the 7 days prior to first dose day of trial drug.

Subjects in the Crofelemer and placebo treatment groups had similar medical histories by SOC and preferred term, and subject histories were consistent with an HIV+ population.

Demography of Long-Term Crofelemer Experience Safety Population - ADVENT
Demographic, baseline characteristics, and medical history were similar in the Long-Term Crofelemer Experience Safety population and the PC phase population (Table 37).

Demography of HIV+ Integrated Safety Population
Demographic characteristics were similar between treatment groups in the HIV+ population (ADVENT, 37554-210, and 37554-209 trials) (Table 38). Most subjects (88%) in each treatment group were male. Mean and median ages in the Crofelemer groups and the placebo group were approximately 42 to 45 years, and the range was 21 to 69 years. White, Black, and Hispanic subjects were well represented in each treatment group, although the crofelemer 250 mg daily group had a lower proportion of White subjects (and conversely, higher proportions of Black and Hispanic subjects) compared with the Crofelemer > 250 mg daily group and the placebo group.

Table 38: Demographics (HIV+ Integrated Safety Population)

Characteristic/ Statistic	Crofelemer 250 mg Daily N = 229	Crofelemer >250 mg Daily N = 467	All Crofelemer N = 696	Placebo N = 274
Age (years)	N = 229	N = 467	N = 696	N = 273
Mean (SD)	44.5 (8.24)	41.8 (7.92)	42.7 (8.12)	42.1 (8.10)
Median (min, max)	45.0 (21-62)	41.0 (21-69)	42.0 (21-69)	42.0 (21-63)
Sex – n (%)				
Male	193 (84.3)	422 (90.4)	615 (88.4)	241 (88.0)
Female	36 (15.7)	45 (9.6)	81 (11.6)	33 (12.0)
Race – n (%)				
White/Caucasian	87 (38.0)	290 (62.1)	377 (54.2)	149 (54.4)
Black/African American	91 (39.7)	110 (23.6)	201 (28.9)	81 (29.6)
Other[a]	50 (21.8)	62 (13.3)	112 (16.1)	42 (15.3)
Asian	0	1 (0.2)	1 (0.1)	0
Ethnicity – n (%)				
Hispanic	48 (21.0)	59 (12.6)	107 (15.4)	39 (14.2)

From Section 2.7, Summary of Clinical Safety, Page 52
Abbreviations: CRF = case report form; HIV+ = human immunodeficiency virus positive; min = minimum; max = maximum; SD = standard deviation.
a. "Other" includes CRF categories Asian, Asian/Pacific Islander, Hispanic, and other races. In the ADVENT CRFs, "Hispanic" was listed as a selectable option for race. In the post-text and in-text demographic tables, ADVENT subjects recorded as "Hispanic" are summarized as an ethnicity and listed in the "Other" category for race.

The mean time since HIV diagnosis was 9 years both in the all Crofelemer group and in the placebo group for the HIV+ Integrated Safety population (ADVENT, 37554-210, and 37554-209 trials) (Table 41). The mean CD4 cell count was similar between the all crofelemer and placebo groups (389.4 vs. 395.5 cells/μL); the mean CD4 cell count was 518.3 cells/μL in the Crofelemer 250 mg daily group and almost two-thirds (63%) of this group had counts ≥ 404. Approximately 60% of subjects in the all Crofelemer and placebo groups had HIV-1 viral loads < 400 copies/mL; 91% of the Crofelemer 250 mg daily group had HIV-1 loads < 400 copies/mL.

Baseline averages for daily bowel movements (watery, loose, and total) during 7 days prior to first dose of trial drug were generally comparable between the all Crofelemer and placebo groups, although the crofelemer 250 mg daily group had a lower mean number of watery stools (2.35) than the crofelemer > 250 mg daily (3.42) and placebo (3.62) groups; the medians were 2.00, 3.00, and 3.00, respectively.

Baseline creatinine clearance was ≥ 60 mL/min in ≥ 96% of subjects in all groups.

Table 39: Baseline Characteristics (HIV+ Integrated Safety Population)

Characteristic/ Statistic	Crofelemer 250 mg Daily N = 229	Crofelemer >250 mg Daily N = 467	All Crofelemer N = 696	Placebo N = 274
Time Since HIV Diagnosis (years)	N = 229	N = 458	N = 687	N = 269
Mean (± SD)	12.28 (6.951)	6.57 (5.814)	8.47 (6.771)	8.50 (7.183)
Median (Min, Max)	11.58 (0.3-29.8)	4.53 (0.1-26.3)	6.28 (0.1-29.8)	5.80 (0.0-29.8)
CD4 Cell Count	N = 229	N = 448	N = 677	N = 266
Mean (± SD)	518.3 (242.02)	323.6 (246.17)	389.4 (261.39)	395.5 (256.77)
Median (Min, Max)	503.0 (95-1232)	293.0 (2-1734)	351.0 (2-1734)	365.0 (4-1298)
CD4 Cell Category, n (%)				
<404	84 (36.7)	304 (65.1)	388 (55.7)	143 (52.2)
≥404	145 (63.3)	144 (30.8)	289 (41.5)	123 (44.9)
Missing	0	19 (4.1)	19 (2.7)	8 (2.9)
HIV-1 Viral Load (HIV copies/mL)				
<400	208 (90.8)	204 (43.7)	412 (59.2)	161 (58.8)
≥400	21 (9.2)	257 (55.0)	278 (39.9)	107 (39.1)
Missing	0	6 (1.3)	6 (0.9)	6 (2.2)
Daily Total Number of Watery Stools	N = 229	N = 466	N = 695	N = 274
Mean (± SD)	2.35 (1.734)	3.42 (3.105)	3.07 (2.775)	3.62 (2.991)
Median (Min, Max)	2.00 (0-11.1)	3.00 (0-25.0)	2.43 (0-25.0)	3.00 (0-18.0)
Daily Total Number of Loose Stools	N = 229	N = 466	N = 695	N = 274
Mean (± SD)	1.75 (1.259)	1.71 (1.638)	1.72 (1.522)	1.54 (1.679)
Median (Min, Max)	1.67 (0-7.7)	1.57 (0-10.0)	1.57 (0-10.0)	1.14 (0-12.0)
Daily Total Number of Stools	N = 229	N = 466	N = 695	N = 274
Mean (± SD)	4.82 (2.491)	5.50 (3.010)	5.28 (2.866)	5.61 (3.432)
Median (Min, Max)	4.43 (0.5-16.1)	5.00 (0-25.0)	4.86 (0-25.0)	5.00 (0-33.0)
Baseline Renal Impairment				
Creatinine Clearance <60	10 (4.4)	13 (2.8)	23 (3.3)	8 (2.9)
Creatinine Clearance ≥60	219 (95.6)	454 (97.2)	673 (96.7)	265 (96.7)
Missing	0	0	0	1 (0.4)

From Section 2.7.4, Summary of Clinical Safety, Page 53
Abbreviations: HIV+ = human immunodeficiency virus positive; LTCE = long-term crofelemer experience; min = minimum; max = maximum; SD = standard deviation.

7.2.2 Explorations for Dose Response

The assessment of efficacy is based on Study ADVENT, which was an adaptive trial design. Stage 1 PC phase was conducted with Crofelemer 125 mg, 250 mg, and 500 mg, bid and the placebo control, respectively. An interim analysis was performed following the PC phase of Stage 1. The consulting statistician performing the data analysis for the interim analysis wrote an Interim Analysis Report to the Independent Analysis Committee (IAC), which was in charge of deciding which Crofelemer dose was

selected for Stage 2. Selection of the dose of Crofelemer was made based on the following criteria:

1. The primary efficacy variable in the ITT population (i.e., clinical response), along with AE and SAE rates in the study.

2. The Crofelemer dose selected for Stage 2 was planned to be the one for which the primary efficacy variable in the ITT population was at least 2.0% greater than the other Crofelemer treatments. If there were safety issues, the decision for dose selection was too complex to pre-specify.

3. If 2 or 3 treatment groups had responder rates that were less than 2% of each other, and there were no safety issues, the lowest of these doses was planned to be selected for Stage 2.

In addition, the Interim Analysis Committee examined unblinded safety information for the trial in order to help select the optimal dose of Crofelemer and identify any potential safety signals. If a significant safety signal was identified, it was communicated to the medical monitor of the trial.

7.2.3 Special Animal and/or In Vitro Testing

No new special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Routine clinical testing in the ADVENT study included hematology, blood chemistry, liver function test, urinalysis, stool test, ECG, HIV parameters, vital signs, adverse events, and physical examinations. Clinical testing in Studies 37554-210 and 37554-209 included similar clinical laboratory parameters and vital signs.

7.2.5 Metabolic, Clearance, and Interaction Workup

In HIV-infected patients in the ADVENT study, at the dose chosen (125 mg bid), less than 1% of plasma sample had quantifiable Crofelemer exposure. This result is consistent with the study of topical mechanism of action at the GI epithelium. Because Crofelemer appears to not be systemically absorbed, metabolic and clearance assessments were not part of the Crofelemer development plan. Concomitant medications were reviewed, and were remarkable for direct interaction with nucleoside analog 3TC at the GI tract. According to the Clinical Pharmacology Review by Dr. Estes, this will not be an issue that would preclude approval.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Crofelemer is a new molecular entity, and its mechanism of action is different from other anti-diarrheal drugs. Information for potential adverse events based on similar drugs is not available.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were considered study drug related.

Two HIV+ patients, 1 taking Crofelemer and 1 taking placebo, died during the trial or within 30 days after trial participation (Table 40).

Table 40: Deaths (HIV+ Integrated Safety Population)

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day	Preferred Term	Related to Drug?	Intensity	Outcome
Placebo-Controlled Treatment Phase							
Placebo BID	HV101-0051-0001	(b) (6)	14	Diffuse large B-cell lymphoma	No	Severe	Fatal
Placebo-Free Extension Phase							
125 mg BID	HV101-0031-0008	(b) (6)	+1	Cardiac arrest	No	Severe	Fatal

From HIV+ Listing 5; Summary of Clinical Safety Page 77
Abbreviation: BID = twice daily; HIV+ = human immunodeficiency virus positive.

A brief narrative for the patient receiving crofelemer is provided as follows:

- Subject HV101-0031-0008 (Crofelemer 125 mg bid group), a 62-year-old White male, had a medical history of HIV, hypertension, coronary artery disease, renal insufficiency and chronic bronchitis secondary to a long history of smoking. The patient had undergone coronary artery bypass surgery in 1999 and had been reportedly using 2 nitrate preparations since the year 2000. The last apparent cardiac diagnostic test was performed on May 29, 2001, and the observed echocardiogram abnormalities included a dilated left ventricle with concentric hypertrophy, wall motion abnormalities, left atrial dilatation, and aortic sclerosis. Although the patient's cardiac disease was considered stable at the time of entry into the study (1st dose of Crofelemer in February 6, 2008), it was reported that

the subject had an episode of chest pain on May 3, 2008, which resolved without medical intervention. On (b) (6) the patient presented to the investigator for the Visit 5 appointment reporting chest pain with dysesthesia along the right arm for the past hour. While waiting for rescue personnel to arrive, the patient collapsed and cardiopulmonary resuscitation was started by the clinic staff. The subject was subsequently transported by ambulance to the hospital but died approximately 2 hours later. No autopsy was performed.

Medical Officer Comment:
The reviewer agrees with the Applicant's assessment that there is not sufficient evidence to support a causal relationship between the death of Patient HV101-0031-0008 and the study drug.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Nonfatal SAEs in ADVENT PC Phase Safety Population

In the ADVENT PC phase, 2 Crofelemer patients (< 1%) experienced SAEs (*Escherichia* sepsis and pneumonia, respectively), each in the 125 mg bid group (Table 41, combined analysis of Stages 1 and 2). In the placebo group, 4 subjects (3%) experienced a total of 5 SAEs (diffuse large B-cell lymphoma, phlebitis, and pneumonia in 1 patient each; and acute pancreatitis and alcohol withdrawal syndrome both in 1 patient). None of the SAEs in either treatment group was regarded by the investigator as drug-related. With the exception of fatal lymphoma in Patient HV101-0051-0001 (placebo group), all SAEs resolved or resolved with sequelae.

Table 41: SAEs (ADVENT PC Phase, Stages 1 and 2 Combined)

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
125 mg BID	0051-0009	11 Oct 2009/ 15 Oct 2009	7	*Escherichia* sepsis	No	Severe	Resolved
125 mg BID	0072-0010	09 Dec 2009/ 16 Dec 2009	21	Pneumonia	No	Mild	Resolved
Placebo BID	0011-0025	13 Apr 2009/ 22 Apr 2009	+1	Phlebitis	No	Severe	Resolved[b]
Placebo BID	0051-0001	21 Jul 2008/ 08 Aug 2008	14	Diffuse large B-cell lymphoma	No	Severe	Fatal[b]
Placebo BID	0056-0014	30 Apr 2009/ 15 May 2009	10	Pneumonia	No	Severe	Resolved
Placebo BID	0084-0008	25 Sep 2009/ 19 Oct 2009	25	Pancreatitis acute	No	Moderate	Resolved
		25 Sep 2009/ 19 Oct 2009	25	Alcohol withdrawal syndrome	No	Severe	Resolved

From ADVENT CSR Listing 16.2.7.2. Summary of Clinical Safety Page 79
Abbreviations: BID = twice daily; CSR = clinical study report; PC = placebo controlled; SAE = serious adverse event.
a. If the date of the SAE was after the last dose date, trial day was calculated as the event date - last dose date and is displayed as "+XX."
b. Subject discontinued trial drug as a result of this SAE.

7.3.2.2 Nonfatal SAEs in Long-Term Crofelemer Experience Safety Population-ADVENT

In the Long-Term Crofelemer Experience Safety population, SAEs occurred in 15 patients (4%) treated with Crofelemer (Table 42). Pneumonia and suicide attempt were the only SAE preferred terms reported for more than 1 patient. Each of the 2 patients with an SAE of suicide attempt (Subjects HV101-0003-0021 and HV101-0084-0008; 125 mg bid group) had a medical history significant for depression, anxiety, and other psychiatric conditions. Of the 2 subjects with pneumonia, Patient HV101-0072-0010 (125 mg bid) had a medical history of pneumonia and tuberculosis and Patient HV101-0003-0003 (> 125 mg bid) had a history of frequent coughing episodes. Patient 0035-0004 (embolic stroke) had a history of hypertension, cardiomyopathy, and abnormal ECG. None of the SAEs were judged by the investigator to be drug-related.

Table 42: SAEs (Long-Term Crofelemer Experience Safety Population - ADVENT)

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
125 mg BID	HV101-0003-0021	06 Nov 2009/ 10 Dec 2009	44	Suicide attempt	No	Severe	Resolved
125 mg BID	HV101-0007-0029	21 Jul 2008/ 20 Aug 2008	22	Tracheobronchitis	No	Severe	Resolved
125 mg BID	HV101-0014-0033	09 May 2010/ 10 May 2010	138	Appendicitis	No	Severe	Resolved
125 mg BID	HV101-0025-0055	18 Aug 2010/ 21 Aug 2010	7	Syncope	No	Moderate	Resolved
125 mg BID	HV101-0031-0008	(b) (6)	+1	Cardiac arrest	No	Severe	Fatal[b]
125 mg BID	HV101-0051-0009	11 Oct 2009/ 15 Oct 2009	7	*Escherichia* sepsis	No	Severe	Resolved
125 mg BID	HV101-0056-0015	22 Feb 2010/ 19 Apr 2010	+13[c]	Gastritis hemorrhagic	No	Moderate	Resolved
125 mg BID	HV101-0057-0017	19 Dec 2009/ 02 Feb 2010	46	Radius fracture	No	Severe	Resolved with sequelae
125 mg BID	HV101-0058-0018	03 Sep 2010/ 05 Sep 2010	74	Gastroenteritis viral	No	Moderate	Resolved
125 mg BID	HV101-0072-0010	09 Dec 2009/ 16 Dec 2009	21	Pneumonia	No	Mild	Resolved
125 mg BID	HV101-0084-0008	25 Oct 2009/ 28 Oct 2009	18	Suicide attempt	No	Severe	Resolved
		09 Nov 2009/ 20 Nov 2009	+4	Cellulitis	No	Severe	Resolved
		10 Nov 2009/ 11 Nov 2009	+5	Suicidal ideation	No	Severe	Resolved
125 mg BID	HV101-1369-0032	03 Dec 2010/ 28 Dec 2010	159	Prostate cancer	No	Moderate	Resolved with sequelae
250 mg BID	HV101-0032-0004	22 Aug 2008/ 26 Aug 2008	110	Depression	No	Mild	Resolved
		20 Sep 2008/ 24 Sep 2008	139	Depression	No	Mild	Resolved
250 mg BID	HV101-0035-0004	26 Oct 2008/ 28 Oct 2008	138	Embolic stroke	No	Severe	Resolved[b]
250 mg BID	HV101-0045-0017	05 Mar 2009/ 07 Mar 2009	161	Gastroenteritis	No	Severe	Resolved
500 mg BID	HV101-0003-0003	29 Feb 2008/ 14 Mar 2008	81	Pneumonia	No	Severe	Resolved
		14 Mar 2008/ 15 Mar 2008	95	Hypotension	No	Moderate	Resolved

From LTCE Listing 3. Summary of Clinical Safety Page 80
Abbreviations: BID = twice daily; LTCE = long-term Crofelemer experience; SAE = serious adverse event.
a. If the date of the SAE was after the last dose date, trial day was calculated as the event date - last dose date and is displayed as "+XX."
b. Subject discontinued trial drug as a result of this SAE.
c. The SAE of gastritis hemorrhagic (Patient HV101-0056-0015) onset > 5 days following discontinuation of drug; this event was therefore not
treatment emergent and was not included in the tabular summaries of SAEs.

7.3.2.3 Nonfatal SAEs in HIV+ Integrated Safety Population

In the HIV+ Integrated Safety population, SAEs occurred in 19 Crofelemer patients (3%) and 6 placebo patients (2%) as shown in Table 43. Most SAE terms were reported for only 1 patient each; anemia, pneumonia, depression, and suicide attempt were each reported for 2 patients (0.3%) in the all Crofelemer group. Both patients with SAEs of depression were receiving Crofelemer > 250 mg daily: Patient HV101-0032-0004 had a history of depression and Patient HV210-004-0263 reported no history of psychiatric issues. Patient HV210-004-0263 also had an SAE of anemia (medical history of anemia, eosinophilia, and leucopenia) as did Patient HV209-001-0506 (medical history of anemia and lymphoma).

Serious AEs in the HIV+ Integrated Safety population resolved or resolved with sequelae except in the 2 subjects who had SAEs with fatal outcomes and Patient HV210-004-0263 (Crofelemer > 250 mg daily) who had anemia, depression, *P. jiroveci* pneumonia, and rectal ulcer all of which started 3 days after last dose of trial drug. Two patients in the Crofelemer > 250 mg daily group had SAEs considered to be possibly related to trial drug by the investigator: Patient HV210-016-0234 had dyspnea and Patient HV210-030-0534 had disorientation, dysarthria, and hallucination.

The date of onset for the SAE of gastritis hemorrhagic (Patient HV101-0056-0015) was > 5 days following discontinuation of drug; this event was not treatment emergent and was not, therefore, included in the tabular summaries of SAEs.

Table 43: SAEs (HIV+ Integrated Safety Population)

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
125 mg BID	HV101-0003-0021	06 Nov 2009/ 10 Dec 2009	44	Suicide attempt	No	Severe	Resolved
125 mg BID	HV101-0007-0029	21 Jul 2008/ 20 Aug 2008	56	Tracheobronchitis	No	Severe	Resolved
125 mg BID	HV101-0014-0033	09 May 2009/ 10 May 2009	138	Appendicitis	No	Severe	Resolved
125 mg BID	HV101-0025-0055	18 Aug 2010/ 21 Aug 2010	37	Syncope	No	Moderate	Resolved
125 mg BID	HV101-0031-0008	(b) (6)	+1	Cardiac arrest	No	Severe	Fatal[b]
125 mg BID	HV101-0051-0009	11 Oct 2009/ 15 Oct 2009	7	*Escherichia* sepsis	No	Severe	Resolved
125 mg BID	HV101-0056-0015[c]	22 Feb 2010/ 19 Apr 2010	+13	Gastritis hemorrhagic	No	Moderate	Resolved
125 mg BID	HV101-0057-0017	19 Dec 2009/ 02 Feb 2010	46	Radius fracture	No	Severe	Resolved with sequelae
125 mg BID	HV101-0058-0018	03 Sep 2010/ 05 Sep 2010	109	Gastroenteritis viral	No	Moderate	Resolved
125 mg BID	HV101-0072-0010	09 Dec 2009/ 16 Dec 2009	21	Pneumonia	No	Mild	Resolved
125 mg BID	HV101-0084-0008	25 Oct 2009/ 28 Oct 2009	55	Suicide attempt	No	Severe	Resolved
		09 Nov 2009/ 20 Nov 2009	+4	Cellulitis	No	Severe	Resolved
		10 Nov 2009/ 11 Nov 2009	+5	Suicidal ideation	No	Severe	Resolved
125 mg BID	HV101-1369-0032	03 Dec 2010/ 28 Dec 2010	159	Prostate cancer	No	Moderate	Resolved with sequelae
250 mg BID	HV101-0032-0004	22 Aug 2008/ 26 Aug 2008	110	Depression	No	Mild	Resolved
		20 Sep 2008/ 24 Sep 2008	139	Depression	No	Mild	Resolved
250 mg BID	HV101-0035-0004	26 Oct 2008/ 28 Oct 2008	173	Embolic stroke	No	Severe	Resolved[b]
250 mg BID	HV101-0045-0017	05 Mar 2009/ 07 Mar 2009	161	Gastroenteritis	No	Severe	Resolved
500 mg BID	HV101-0003-0003	29 Feb 2008/ 14 Mar 2008	81	Pneumonia	No	Severe	Resolved
		14 Mar 2008/ 15 Mar 2008	95	Hypotension	No	Moderate	Resolved
500 mg QID	HV209-001-0506	31 Jul 1997/ 02 Aug 1997	+5	Anemia	No	Moderate	Resolved

Continued

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
250 mg QID	HV210-004-0263	25 Jul 1998/ ongoing	+3	Anemia	No	Severe	Not resolved
		25 Jul 1998/ ongoing	+3	Depression	No	Severe	Not resolved
		25 Jul 1998/ ongoing	+3	*Pneumocystis jiroveci* pneumonia	No	Severe	Not resolved
		25 Jul 1998/ ongoing	+3	Rectal ulcer	No	Severe	Not resolved
250 mg QID	HV210-016-0234	01 Jul 1998/ 09 Jul 1998	6	Dyspnea	Yes	Severe	Resolved[b]
250 mg QID	HV210-030-0534	05 Aug 1998/ ongoing	6	Disorientation	Yes	Severe	Not recovered[b]
		05 Aug 1998/ 14 Aug 1998	6	Dysarthria	Yes	Severe	Not recovered[b]
		05 Aug 1998/ ongoing	6	Hallucination	Yes	Severe	Not recovered[b]
Placebo BID	HV101-0011-0025	13 Apr 2009/ 22 Apr 2009	+1	Phlebitis	No	Severe	Resolved[b]
Placebo BID	HV101-0051-0001	21 Jul 2008/ 08 Aug 2008	14	Diffuse large B-cell lymphoma	No	Severe	Fatal[b]
Placebo BID	HV101-0056-0014	30 Apr 2009/ 15 May 2009	10	Pneumonia	No	Severe	Resolved
Placebo BID	HV101-0084-0008	25 Sep 2009/ 19 Oct 2009	25	Pancreatitis acute	No	Moderate	Resolved
		25 Sep 2009/ 19 Oct 2009	25	Alcohol withdrawal syndrome	No	Severe	Resolved
Placebo QID	HV210-0012-0541	04 Aug 1998/ 04 Aug 1998	5	Drug hypersensitivity	No	Severe	Resolved
Placebo QID	HV210-0024-0537	14 Aug 1998/ 14 Aug 1998	15	Intracranial aneurysm	No	Severe	Resolved

From HIV+ Listing 3 and 37554-209, Listing 2. Summary of Clinical Safety Page 82
Abbreviations: BID = twice daily; HIV+ = human immunodeficiency virus positive; QID = 4 times daily; SAE = serious adverse event.
a. If the date of the SAE was after the last dose date, trial day was calculated as the event date - last dose date and is displayed as "+XX."
b. Subject discontinued trial drug as a result of this SAE.
c. The date of onset for the SAE of gastritis hemorrhagic (Subject HV101-0056-0015) was > 5 days following discontinuation of drug; this event was not treatment emergent and was not, therefore, included in the tabular summaries of SAEs.

Medical Officer Comments:
There is not sufficient evidence to support a causal relationship between the above non-fatal SAEs in the HIV Positive Integrated Safety Population and the study drug.

There is no report of allergic reactions in the HIV integrated safety population (696 patients).

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Dropouts in ADVENT PC Phase Safety Population

No Crofelemer-treated patient had a TEAE leading to trial drug discontinuation in the PC phase of the ADVENT trial. A total of 4 placebo patients (3%) experienced a TEAE leading to trial drug discontinuation (i.e., Phlebitis, rash pruritic, gynecomastia, and diffuse large B-cell lymphoma). Two of these events (rash pruritic in Subject HV101-0015-0009 and gynecomastia in Patient HV101-0044-0006) were considered by the investigator to be possibly related to trial drug and were ongoing at the end of the trial.

7.3.3.2 Dropouts in Long-Term Crofelemer Experience Safety Population - ADVENT

In the Long-Term Crofelemer Experience Safety population, 6 patients (2%) had TEAEs leading to trial drug discontinuation (Table 46). Five of these patients were in the 125 mg bid group (2%) and discontinued due to the following events: abscess soft tissue, blood alkaline phosphatase increased, cardiac arrest, tachycardia, and thrombocytopenia. One patient in the > 125 mg bid group (1%) discontinued as the result of an embolic stroke. Two of these events (blood alkaline phosphatase increased in Patient HV101-0011-0033 and thrombocytopenia in Patient HV101-0072-0002) were considered by the investigator to be possibly related to trial drug. The events of blood alkaline phosphatase increased and tachycardia were ongoing at the end of trial.

Plasma concentrations of Crofelemer were below the LOQ (50 ng/mL) during the course of the study for each of the 6 patients who had had TEAEs leading to trial drug discontinuation [Crofelemer Plasma Concentrations Analytical Report (ADVENT)].

Of note, Patient HV101-0072-0002 (thrombocytopenia) had a history of deep vein thrombosis, and was receiving concomitant warfarin sodium (2.5 mg daily) during the trial at the time of the event. Patient HV101-0011-0033 (blood alkaline phosphatase increased) first experienced elevated alkaline phosphatase at the end of placebo treatment in the PC phase (188 U/L; normal range: 31 to 129 U/L) and discontinued drug early in the PF phase due to continued elevations in this laboratory parameter.

Medical Officer Comments:
There is not sufficient evidence to support a causal relationship between Crofelemer treatment and the dropouts.

Table 44: TEAEs Leading to Trial Drug Discontinuation (Long-Term Crofelemer Experience Safety Population - ADVENT)

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
125 mg BID	HV101-0011-0033	09 Nov 2009/ Ongoing	1	Blood alkaline phosphatase increased	Yes	Severe	Not Resolved
125 mg BID	HV101-0011-0053	06 Aug 2010/ 06 Nov 2010	54	Pain in extremity[b]	No	Mild	Resolved
125 mg BID	HV101-0031-0008	(b) (6)	+1	Cardiac arrest[c]	No	Severe	Fatal
125 mg BID	HV101-0053-0005	10 Feb 2009/ 16 Feb 2009	51	Abscess soft tissue	No	Moderate	Resolved
125 mg BID	HV101-0072-0002	08 Dec 2009/ 05 Jan 2010	64	Thrombocytopenia	Yes	Moderate	Resolved
125 mg BID	HV101-0078-0009	09 Feb 2010/ Ongoing	43	Tachycardia	No	Moderate	Not Resolved
250 mg BID	HV101-0035-0004	26 Oct 2008/ 28 Oct 2008	138	Embolic stroke[c]	No	Severe	Resolved

From LTCE Listing 4; Summary of Clinical Safety Page 86
Abbreviations: BID = twice daily; LTCE = long-term crofelemer experience; SAE = serious adverse event; TEAE = treatment emergent adverse event.
a. If the date of the SAE was after the last dose date, trial day was calculated as the event date - last dose date and is displayed as "+XX."
b. For Patient 0011-0053 in the Crofelemer 125 mg group, a TEAE of "pain in extremity" was mistakenly recorded as a TEAE leading to trial drug discontinuation in the subject case report form. This patient continued on trial drug after onset of the TEAE of "pain in extremity" and did not discontinue prematurely from the trial.
c. Event was also considered to be an SAE.

7.3.3.3 Dropouts in HIV+ Integrated Safety Population

In the HIV+ Integrated Safety population, 15 Crofelemer patients (2%), 5 in the 250 mg daily group (2%) and 10 in the > 250 mg daily group (2%), and 7 placebo subjects (3%) experienced TEAEs leading to trial drug discontinuation (Table 45). No TEAE that resulted in trial drug discontinuation was observed for more than 1 subject. The most common SOC associated with TEAEs resulting in trial drug discontinuation were GI disorders and these resulted in discontinuation of similar proportions of patients from the Crofelemer and placebo groups (all Crofelemer 0.4%, placebo 0.7%). The event of cardiac arrest in Patient HV101-0031-0008 (Crofelemer > 250 mg daily) and the event of diffuse large B-cell lymphoma in Patient HV101-0051-0001 (placebo) resulted in fatal outcomes. A total of 6 Crofelemer subjects and 2 placebo subjects had TEAEs leading to trial drug discontinuation that were ongoing at the end of trial participation. Nine patients taking Crofelemer and 5 patients taking placebo had TEAEs that resulted in trial drug discontinuation that were considered by the investigators to be possibly or probably related to trial drug.

Of note, Patient HV210-030-0534 (disorientation, dysarthria, and hallucination) had a history of bipolar disorder and panic attacks, as well as cluster seizures and encephalopathy.

Table 45: TEAEs Leading to Trial Drug Discontinuation (HIV+ Integrated Safety Population)

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
125 mg BID	HV101-0011-0033	09 Nov 2009/ Ongoing	35	Blood alkaline phosphatase increased	Yes	Severe	Not Resolved
125 mg BID	HV101-0031-0008	(b) (6)	+1	Cardiac arrest[b]	No	Severe	Fatal
125 mg BID	HV101-0053-0005	10 Feb 2009/ 16 Feb 2009	86	Abscess soft tissue	No	Moderate	Resolved
125 mg BID	HV101-0072-0002	08 Dec 2009/ 05 Jan 2010	64	Thrombocytopenia	Yes	Moderate	Resolved
125 mg BID	HV101-0078-0009	09 Feb 2010/ Ongoing	43	Tachycardia	No	Moderate	Not Resolved
250 mg BID	HV101-0035-0004	26 Oct 2008/ 28 Oct 2008	173	Embolic stroke[b]	No	Severe	Resolved
250 mg QID	HV210-004-0205	20 May 1998/ 21 May 1998	6	Viral infection	Yes	Moderate	Resolved
250 mg QID	HV210-005-0131	06 Jun 1998/ ongoing	11	Hemorrhoids	Yes	Moderate	Not resolved
250 mg QID	HV210-016-0234	01 Jul 1998/ 09 Jul 1998	6	Dyspnea[b]	Yes	Severe	Resolved
250 mg QID	HV210-030-0534	05 Aug 1998/ ongoing	6	Disorientation[b]	Yes	Severe	Not resolved
		05 Aug 1998/ 14 Aug 1998	6	Dysarthria[b]	Yes	Severe	Not resolved
		05 Aug 1998/ ongoing	6	Hallucination[b]	Yes	Severe	Not resolved
500 mg QID (tab)	HV210-004-0153	12 May 1998/ 13 May 1998	6	Food allergy	Yes	Moderate	Resolved
500 mg QID (tab)	HV210-004-0355	08 Jul 1998/ ongoing	7	Platelet count decreased	No	Moderate	Not resolved
500 mg QID (beads/tab)	HV210-005-0293	24 Jun 1998/ ongoing	1	Giardiasis	No	Moderate	Not resolved
500 mg QID (tab)	HV210-014-0388	04 Aug 1998/ 05 Aug 1998	1	Abdominal pain	Yes	Moderate	Resolved
		04 Aug 1998/ 05 Aug 1998	1	Diarrhea	Yes	Moderate	Resolved

Continued

Treatment Group	Subject Number	Date of Onset/ End Date	Trial Day[a]	Preferred Term	Related to Drug?	Intensity	Outcome
500 mg QID (tab)	HV210-019-0443	16 Aug 1998/ 20 Aug 1998	11	Nausea	Yes	Severe	Resolved
		16 Aug 1998/ 20 Aug 1998	11	Vomiting	Yes	Severe	Resolved
Placebo BID	HV101-0011-0025	13 Apr 2009/ 22 Apr 2009	+1	Phlebitis[b]	No	Severe	Resolved
Placebo BID	HV101-0015-0009	04 May 2009/ Ongoing	8	Rash pruritic	Yes	Moderate	Not Resolved
Placebo BID	HV101-0044-0006	11 Apr 2008/ Ongoing	5	Gynecomastia	Yes	Moderate	Not Resolved
Placebo BID	HV101-0051-0001	21 Jul 2008/ 08 Aug 2008	14	Diffuse large B-cell lymphoma[b]	No	Severe	Fatal
Placebo QID	HV210-019-0191	13 Jul 1998/ 21 Jul 1998	5	Rash	Yes	Moderate	Resolved
Placebo QID	HV210-020-0302	07 Jul 1998/ 10 Aug 1998	13	Diarrhea	Yes	Moderate	Resolved
Placebo QID	HV210-024-0537	19 Aug 1998/ 03 Sep 1998	20	Constipation	Yes	Mild	Resolved

From LTCE Listing 4; Summary of Clinical Safety Page 87
Abbreviations: BID = twice daily; HIV+ = human immunodeficiency virus positive; QID = 4 times daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a. If the date of the SAE was after the last dose date, trial day was calculated as the event date - last dose date and is displayed as "+XX."
b. Event was also considered to be an SAE.
Note: The number of subjects listed in this in-text table differs from the source listing. For Subject 0011-0053 in the Crofelemer 125 mg group, a TEAE of "pain in extremity" was mistakenly recorded as a TEAE leading to trial drug discontinuation in the subject case report form. This subject continued on trial drug after onset of the TEAE of "pain in extremity" and did not discontinue prematurely from the trial.

7.3.4 Significant Adverse Events

No AEs of special interest were identified from clinical trials in HIV+ individuals with diarrhea.

7.3.5 Submission Specific Primary Safety Concerns

No specific primary safety concerns with this submission.

The concern that anti-diarrhea treatment by Crofelemer may delay the diagnosis and treatment of pathogen-specific diarrhea will be adequately addressed in the labeling.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Common AEs in ADVENT PC Phase Safety Population

The percentage of subjects who experienced TEAEs during the PC phase of the ADVENT trial was lower in all Crofelemer groups compared with the placebo group (27% vs. 33%), and similar in the Crofelemer 125 mg bid group compared with the placebo group (35% vs. 33%). Treatment-emergent AEs by SOC and by preferred term occurred with similar frequencies between Crofelemer- and placebo-treated patients during the PC phase (Table 46). Treatment-emergent AEs in the PC phase occurred most frequently in the infections and infestations (all Crofelemer 10%, placebo 11%) and GI disorders (9% vs. 6%) SOCs. The most frequently occurring TEAEs in Crofelemer-treated subjects were upper respiratory tract infections (all Crofelemer 3%, placebo 3%) and urinary tract infections (2% vs. 1%). All other TEAEs were experienced by ≤ 3 subjects treated with Crofelemer (N=226). In the placebo group (N=137), the most frequently occurring TEAEs were upper respiratory tract infections (all Crofelemer 3%, placebo 3%), blood bilirubin increased (1% vs. 2%), and blood bilirubin unconjugated increased (1% vs. 2%).

Table 46: TEAEs Occurring in ≥ 3 Subjects Treated with Crofelemer or Placebo (ADVENT PC Phase, Stages 1 and 2 Combined)

System Organ Class Preferred Term	Crofelemer 125 mg BID N = 130 n (%)	Crofelemer 250 mg BID N = 54 n (%)	Crofelemer 500 mg BID N = 42 n (%)	All Crofelemer N = 226 n (%)	Placebo BID N = 137 n (%)
Any TEAEs	45 (34.6)	10 (18.5)	7 (16.7)	62 (27.4)	45 (32.8)
Gastrointestinal Disorders					
Abdominal pain	2 (1.5)	0	1 (2.4)	3 (1.3)	1 (0.7)
Constipation	2 (1.5)	1 (1.9)	0	3 (1.3)	1 (0.7)
Dyspepsia	2 (1.5)	0	1 (2.4)	3 (1.3)	0
Flatulence	2 (1.5)	1 (1.9)	0	3 (1.3)	0
Nausea	1 (0.8)	1 (1.9)	1 (2.4)	3 (1.3)	1 (0.7)
General Disorders and Administration Site Conditions					
Fatigue	1 (0.8)	1 (1.9)	1 (2.4)	3 (1.3)	0
Infections and Infestations					
Upper respiratory tract infection	5 (3.8)	1 (1.9)	0	6 (2.7)	4 (2.9)
Urinary tract infection	3 (2.3)	1 (1.9)	0	4 (1.8)	1 (0.7)
Herpes zoster	2 (1.5)	1 (1.9)	0	3 (1.3)	0
Investigations					
Blood bilirubin increased	3 (2.3)	0	0	3 (1.3)	3 (2.2)
Blood bilirubin unconjugated increased	2 (1.5)	0	0	2 (0.9)	3 (2.2)
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	2 (1.5)	0	1 (2.4)	3 (1.3)	0
Nervous System Disorders					
Headache	1 (0.8)	1 (1.9)	1 (2.4)	3 (1.3)	1 (0.7)

From ADVENT CSR Table 14.3.1.2.1; corresponding ADVENT CSR Listing 16.2.7.1; Summary of Clinical Safety Page 59
Abbreviations: BID = twice daily; CSR = clinical study report; PC = placebo controlled; TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity. The TEAEs are presented alphabetically by system organ class, and by descending order of frequency among all Crofelemer-treated subjects within each system organ class.

Treatment-emergent AEs that occurred at higher incidence in a Crofelemer dose group than in the placebo group were reported for a small proportion of patients (<4%) and are events commonly observed in HIV individuals or in the general population. Events that occurred in ≥ 1% of patients and had a higher incidence with Crofelemer than with placebo included abdominal pain, constipation, dyspepsia, flatulence, fatigue, upper respiratory tract infection, urinary tract infection, herpes zoster, and arthralgia (Table 47). The incidence of each of these events was < 2-fold higher in Crofelemer-treated subjects than in placebo-treated subjects. The duration of exposure to trial drug was approximately the same in the Crofelemer and placebo groups in the 4-week PC phase of the ADVENT trial.

Table 47: TEAEs Occurring in ≥ 1% of Subjects with Higher Incidence in Crofelemer 125 mg bid than in Placebo - ADVENT (PC Phase, Safety Population)

System Organ Class Preferred Term	Crofelemer 125 mg BID N = 130 n (%)	All Crofelemer N = 226 n (%)	Placebo BID N = 137 n (%)
Any TEAEs	45 (35)	62 (27)	45 (33)
Gastrointestinal Disorders			
Abdominal pain	2 (2)	3 (1)	1 (1)
Constipation	2 (2)	3 (1)	1 (1)
Dyspepsia	2 (2)	3 (1)	0
Flatulence	2 (2)	3 (1)	0
Infections and Infestations			
Upper respiratory tract infection	5 (4)	6 (3)	4 (3)
Urinary tract infection	3 (2)	4 (2)	1 (1)
Herpes zoster	2 (2)	3 (1)	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	2 (2)	3 (1)	0

From ADVENT CSR Table 14.3.1.8.; Summary of Clinical Safety Page 60
Abbreviations: BID = twice daily; CSR = clinical study report; PC = placebo controlled; TEAE = treatment-emergent adverse event.
Note: This table includes TEAEs that occurred at an incidence of 1% or more in the source table prior to rounding.

Treatment-emergent AEs that occurred in < 1% of subjects, in at least 2 subjects who received Crofelemer, and with higher incidence in Crofelemer than in placebo by SOC (with incidence in all crofelemer, placebo) were the following:

- Gastrointestinal Disorders: hemorrhoids (0.9%, 0)
- Infections and Infestations: bronchitis (0.9%, 0), onychomycosis (0.9%, 0.7%),
- Injury, Poisoning and Procedural Complications: contusion (0.9%, 0), procedural pain (0.9%, 0)
- Investigations: alanine aminotransferase increased (0.9%, 0.7%)
- Musculoskeletal and Connective Tissue Disorders: muscle spasms (0.9%, 0.7%), musculoskeletal pain (0.9%, 0.7%)
- Skin and Subcutaneous Tissue Disorders: acne (0.9%, 0)

TEAEs by Intensity in ADVENT PC Phase

In the ADVENT PC Phase Safety population, most TEAEs were mild or moderate in intensity in each treatment group. During the PC phase, only 3 subjects (1%) in the combined Crofelemer treatment groups (N=226) experienced severe TEAEs (back pain, *Escherichia* sepsis, and musculoskeletal pain in 1 subject each). In the placebo group, 7 severe TEAEs were recorded in 5 subjects (4%): diffuse large B-cell lymphoma, hepatic failure, and acute renal failure (all in 1 subject), and alcohol withdrawal syndrome, gastroenteritis, phlebitis, and pneumonia (in 1 subject each). None of the severe TEAEs in the PC phase was considered by the investigator to be drug related.

Table 48: Summary of All Severe TEAEs (ADVENT PC Phase, Stages 1 and 2 Combined)

Preferred Term	Crofelemer 125 mg BID N = 130 n (%)	Crofelemer 250 mg BID N = 54 n (%)	Crofelemer 500 mg BID N = 42 n (%)	All Crofelemer N = 226 n (%)	Placebo BID N = 137 n (%)
Any Severe TEAEs	2 (1.5)	1 (1.9)	0	3 (1.3)	5 (3.6)
Back pain	1 (0.8)	0	0	1 (0.4)	0
Escherichia sepsis	1 (0.8)	0	0	1 (0.4)	0
Musculoskeletal pain	0	1 (1.9)	0	1 (0.4)	0
Alcohol withdrawal syndrome	0	0	0	0	1 (0.7)
Diffuse large B-cell lymphoma	0	0	0	0	1 (0.7)
Gastroenteritis	0	0	0	0	1 (0.7)
Hepatic failure	0	0	0	0	1 (0.7)
Phlebitis	0	0	0	0	1 (0.7)
Pneumonia	0	0	0	0	1 (0.7)
Renal failure acute	0	0	0	0	1 (0.7)

From Section 2.7.4, Summary of Clinical Safety, Page 61
Abbreviations: BID = twice daily; CSR = clinical study report; PC = placebo controlled; TEAE = treatment-emergent adverse event.
Note: TEAEs are presented by descending order of frequency among all crofelemer-treated subjects by preferred term or alphabetically for events occurring in the same percentage of subjects.

TEAEs by Relationship to Trial Drug Per Investigator in ADVENT PC Phase

The incidence of drug-related TEAEs (i.e., as determined by the investigator) was low in the ADVENT PC phase for all Crofelemer subjects (6%) and for placebo subjects (4%) (Table 49, combined analysis of Stages 1 and 2). The only drug-related TEAEs that occurred in > 1 Crofelemer-treated subject in the PC phase were dyspepsia and flatulence (3 subjects each, 1%), and constipation and muscle spasms (2 subjects each, 1%).

Table 49: Drug-Related TEAEs Occurring in > 1 Subject In a Crofelemer or Placebo Dose Group (ADVENT PC Phase, Stages 1 and 2 Combined)

System Organ Class Preferred Term	Crofelemer 125 mg BID N = 130 n (%)	Crofelemer 250 mg BID N = 54 n (%)	Crofelemer 500 mg BID N = 42 n (%)	All Crofelemer N = 226 n (%)	Placebo BID N = 137 n (%)
Any Drug-related TEAEs	9 (6.9)	2 (3.7)	2 (4.8)	13 (5.8)	5 (3.6)
Gastrointestinal Disorders					
Dyspepsia	2 (1.5)	0	1 (2.4)	3 (1.3)	0
Flatulence	2 (1.5)	1 (1.9)	0	3 (1.3)	0
Constipation	2 (1.5)	0	0	2 (0.9)	1 (0.7)
Musculoskeletal and Connective Tissue Disorders					
Muscle spasms	1 (0.8)	1 (1.0)	0	2 (0.9)	0

From Section 2.7.4, Summary of Clinical Safety, Page 62
Abbreviations: BID = twice daily; CSR = clinical study report; PC = placebo controlled; TEAE = treatment-emergent adverse event.

Note: TEAEs are presented alphabetically by system organ class, and by descending order of frequency among all Crofelemer treated subjects within each system organ class. If a subject experienced more than 1 adverse event, the subject was counted only once for that preferred term or system organ class

7.4.1.2 Common AEs in Long-Term Safety Population - ADVENT

In the Long-Term Crofelemer Experience Safety population, the profile of TEAEs by SOC and by preferred term in the all Crofelemer group was qualitatively similar to the profile observed in the all Crofelemer group and the placebo group during the PC phase. Crofelemer exposure was > 6-fold longer in the long-term population compared with the PC phase population, and the percentages of subjects experiencing TEAEs were therefore higher. After adjustment for exposure duration (event/PEY), the incidence of TEAEs was comparable to or lower in the long term population compared with the PC phase population.

Among all Crofelemer-treated subjects, 60% (212/352) experienced a TEAE in the Long-Term Crofelemer Experience Safety population, and the incidence of TEAEs was similar in each dose group (range: 55% to 63%). Consistent with the PC phase, TEAEs occurred most frequently for all Crofelemer subjects in the infections and infestations (29%) and GI disorders (18%) SOCs. The most frequently occurring TEAEs (≥ 3%) in all Crofelemer subjects were as follows: upper respiratory infection (5%); and nausea, bronchitis, nasopharyngitis, cough, alanine aminotransferase increased, aspartate aminotransferase increased, flatulence, and headache (3% each) (Table 50). The majority of these events are frequently observed in the HIV+ population or in the general population.

Table 50: TEAEs Occurring in ≥ 2% of Subjects in Any Group (Long-Term Crofelemer Experience Safety Population – ADVENT)

System Organ Class Preferred Term	Crofelemer 125 mg BID N = 229 n (%)	Crofelemer >125 mg BID N = 123 n (%)	All Crofelemer N = 352 n (%)
Any TEAEs	145 (63.3)	67 (54.5)	212 (60.2)
Gastrointestinal Disorders			
Nausea	6 (2.6)	5 (4.1)	11 (3.1)
Flatulence	7 (3.1)	2 (1.6)	9 (2.6)
Abdominal pain	4 (1.7)	3 (2.4)	7 (2.0)
Hemorrhoids	5 (2.2)	1 (0.8)	6 (1.7)
Abdominal distension	5 (2.2)	0	5 (1.4)
Gastroesophageal reflux disease	0	3 (2.4)	3 (0.9)
General Disorders and Administration Site Conditions			
Fatigue	2 (0.9)	5 (4.1)	7 (2.0)
Infections and Infestations			
Upper respiratory tract infection	13 (5.7)	5 (4.1)	18 (5.1)
Nasopharyngitis	5 (2.2)	7 (5.7)	12 (3.4)
Bronchitis	9 (3.9)	2 (1.6)	11 (3.1)
Urinary tract infection	5 (2.2)	3 (2.4)	8 (2.3)
Giardiasis	5 (2.2)	0	5 (1.4)
Viral infection	0	3 (2.4)	3 (0.9)
Investigations			
Alanine aminotransferase increased	5 (2.2)	5 (4.1)	10 (2.8)
Aspartate aminotransferase increased	3 (1.3)	6 (4.9)	9 (2.6)
Blood bilirubin increased	7 (3.1)	1 (0.8)	8 (2.3)
Musculoskeletal and Connective Tissue Disorders			
Back pain	6 (2.6)	2 (1.6)	8 (2.3)
Arthralgia	6 (2.6)	1 (0.8)	7 (2.0)
Musculoskeletal pain	5 (2.2)	2 (1.6)	7 (2.0)
Nervous System Disorders			
Headache	4 (1.7)	5 (4.1)	9 (2.6)
Psychiatric Disorders			
Anxiety	5 (2.2)	0	5 (1.4)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	8 (3.5)	3 (2.4)	11 (3.1)

From LTCE Table 2.8.1; corresponding LTCE Listing 2.; Summary of Clinical Safety Page 63
Abbreviations: BID = twice daily; LTCE = long-term crofelemer experience; TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity. The TEAEs are presented alphabetically by system organ class, and by descending order of frequency among all Crofelemer-treated subjects within each system organ class.

TEAEs by Intensity in Long-Term Safety Population

In the Long-Term Crofelemer Experience Safety population, most TEAEs were mild or moderate in intensity in each treatment group. A total of 18 of the 352 Crofelemer subjects (5%) experienced severe TEAEs (Table 51). All severe TEAEs in this population occurred in only 1 subject each, with the exception of suicide attempt in 2 subjects in the 125 mg bid dose group (Subjects HV101-0003-0021 and HV101-0084-0008; these events were also SAEs, and back pain in 2 subject (Subjects HV101-0072-0031 and HV101-0072-0035). Each of the subjects with back pain had an ongoing medical history of back pain when they entered the trial. The only severe TEAE in the Long-Term Crofelemer Experience Safety population considered possibly related to trial drug by the investigator was blood alkaline phosphatase increased in Subject HV101-0011-0033 (125 mg bid group). This event was not an SAE, but led to trial drug discontinuation approximately 10 days following onset. This subject experienced elevated alkaline phosphatase at the end of the PC phase (188 U/L; normal range: 31 to 129 U/L). Three days later this subject experienced pollakiuria, and diagnosed as nephrolithiasis.

Table 51: All Severe TEAEs (Long-Term Crofelemer Experience - ADVENT)

Preferred Term	Crofelemer 125 mg BID N = 229 n (%)	Crofelemer >125 mg BID N = 123 n (%)	All Crofelemer N = 352 n (%)
Any Severe TEAEs	13 (5.7)	5 (4.1)	18 (5.1)
Back pain	2 (0.9)	0	2 (0.6)
Suicide attempt	2 (0.9)	0	2 (0.6)
Appendicitis	1 (0.4)	0	1 (0.3)
Aspartate aminotransferase increased	0	1 (0.8)	1 (0.3)
Blood alkaline phosphatase increased	1 (0.4)	0	1 (0.3)
Cardiac arrest	1 (0.4)	0	1 (0.3)
Cellulitis	1 (0.4)	0	1 (0.3)
Chronic obstructive pulmonary disease	1 (0.4)	0	1 (0.3)
Embolic stroke	0	1 (0.8)	1 (0.3)
Escherichia sepsis	1 (0.4)	0	1 (0.3)
Furuncle	1 (0.4)	0	1 (0.3)
Gastroenteritis	0	1 (0.8)	1 (0.3)
Intracardiac thrombus	0	1 (0.8)	1 (0.3)
Musculoskeletal pain	0	1 (0.8)	1 (0.3)
Pneumonia	0	1 (0.8)	1 (0.3)
Radius fracture	1 (0.4)	0	1 (0.3)
Renal failure acute	0	1 (0.8)	1 (0.3)
Sciatica	1 (0.4)	0	1 (0.3)
Suicidal ideation	1 (0.4)	0	1 (0.3)
Toothache	1 (0.4)	0	1 (0.3)
Tracheobronchitis	1 (0.4)	0	1 (0.3)

From LTCE Table 2.6; corresponding LTCE Listing 2; Summary of Clinical Safety Page 65
Abbreviations: BID = twice daily; LTCE = long-term Crofelemer experience; TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity. The TEAEs are presented descending order of frequency among all Crofelemer-treated subjects.

TEAEs by Relationship to Trial Drug Per Investigator

Drug-related TEAEs (i.e., as determined by the investigator) were reported for 11% of all Crofelemer-treated subjects in the Long-Term Crofelemer Experience Safety population (Table 52). Drug-related TEAEs that occurred in ≥ 1% of subjects who received Crofelemer were as follows: flatulence (3%); and dyspepsia, nausea, abdominal distension, constipation, and ALT increased (1% each). When adjusted for exposure duration (event/PEY), the incidence of drug-related TEAEs was similar between the ADVENT PC Phase and the ADVENT Long-Term Crofelemer Experience populations.

Table 52: Drug-Related TEAEs Occurring in ≥ 1% of All Crofelemer-Treated Subjects (Long-Term Crofelemer Experience - ADVENT)

System Organ Class Preferred Term	Crofelemer 125 mg BID N = 229 n (%)	Crofelemer >125 mg BID N = 123 n (%)	All Crofelemer N = 352 n (%)
Any Drug-related TEAEs	27 (11.8)	11 (8.9)	38 (10.8)
Gastrointestinal Disorders			
Flatulence	7 (3.1)	2 (1.6)	9 (2.6)
Dyspepsia	3 (1.3)	2 (1.6)	5 (1.4)
Nausea	3 (1.3)	2 (1.6)	5 (1.4)
Abdominal distension	4 (1.7)	0	4 (1.1)
Constipation	4 (1.7)	0	4 (1.1)
Investigations			
Alanine aminotransferase increased	3 (1.3)	1 (0.8)	4 (1.1)

From Section 2.7.4, Summary of Clinical Safety, Page 66
Abbreviations: BID = twice daily; LTCE = long-term crofelemer experience; TEAE = treatment-emergent adverse event.
Note: TEAEs are presented alphabetically by system organ class, and by descending order of frequency among all crofelemer treated subjects within each system organ class. If a subject experienced more than 1 adverse event, the subject was counted only once for that preferred term or system organ class.

7.4.1.3 Common AEs in HIV+ Integrated Safety Population

In the HIV+ Integrated Safety population, the profile of TEAEs by SOC and by preferred term in the all Crofelemer and placebo groups was qualitatively similar to the profile observed in the all Crofelemer and placebo groups during the ADVENT PC phase. Trial drug exposure was 9-fold greater in the all Crofelemer group (149.4 PEY) compared to the placebo group (16.6 PEY), approximately 5-fold greater in the Crofelemer 250 mg daily group (88.5 PEY) compared to the placebo group, and almost 4-fold greater in the Crofelemer > 250 mg daily group (3.7-fold; 60.9 PEY) compared to the placebo group in this population. After adjustment for exposure duration (event/PEY), the incidences of TEAEs in the Crofelemer groups were comparable to or lower than in the placebo group.

Among all Crofelemer-treated subjects, 55% (383/696) experienced a TEAE in the HIV+ Integrated Safety population; the incidence of TEAEs was lower in the Crofelemer 250 mg daily group (145/88.7 PEY=1.6 events/PEY) compared to the Crofelemer > 250 mg daily (238/60.9 PEY=3.9 events/PEY) and placebo (100/16.6 PEY=6.0 events/PEY) groups. Treatment-emergent AEs occurred most frequently for all Crofelemer subjects in the infections and infestations (all Crofelemer 20%, placebo 8%), GI disorders (16%, 9%), and nervous system disorders (13%, 12%) SOCs. The most frequently occurring TEAEs (≥ 3%) in all Crofelemer subjects were as follows: headache (all Crofelemer 9%, placebo 10%); and insomnia, upper respiratory infection, and nausea (each 3%, 2%)

(Table 53). The majority of these events are frequently observed in the HIV+ population or in the general population. The common (≥1%) TEAEs reported at higher incidence with Crofelemer than with placebo in the integrated HIV+ population were comparable to those observed in the ADVENT PC phase.

Table 53: TEAEs Occurring in ≥ 2% of Subjects in Any Group (HIV+ Integrated Safety Population)

System Organ Class Preferred Term	Crofelemer 250 mg Daily N = 229 n (%)	Crofelemer >250 mg Daily N = 467 n (%)	All Crofelemer N = 696 n (%)	Placebo N = 274 n (%)
Any TEAEs	145 (63.3)	238 (51.0)	383 (55.0)	100 (36.5)
Gastrointestinal Disorders				
Nausea	6 (2.6)	12 (2.6)	18 (2.6)	4 (1.5)
Dyspepsia	4 (1.7)	12 (2.6)	16 (2.3)	2 (0.7)
Flatulence	7 (3.1)	7 (1.5)	14 (2.0)	3 (1.1)
Abdominal pain	4 (1.7)	10 (2.1)	14 (2.0)	2 (0.7)
Abdominal distension	5 (2.2)	2 (0.4)	7 (1.0)	1 (0.4)
Hemorrhoids	5 (2.2)	4 (0.9)	9 (1.3)	0
General Disorders and Administration Site Conditions				
Pyrexia	2 (0.9)	14 (3.0)	16 (2.3)	2 (0.7)
Infections and Infestations				
Upper respiratory tract infection	13 (5.7)	8 (1.7)	21 (3.0)	4 (1.5)
Nasopharyngitis	5 (2.2)	11 (2.4)	16 (2.3)	2 (0.7)
Bronchitis	9 (3.9)	4 (0.9)	13 (1.9)	0
Urinary tract infection	5 (2.2)	3 (0.6)	8 (1.1)	2 (0.7)
Giardiasis	5 (2.2)	1 (0.2)	6 (0.9)	0
Investigations				
Alanine aminotransferase increased	5 (2.2)	5 (1.3)	10 (1.4)	3 (1.1)
Blood bilirubin increased	7 (3.1)	1 (0.2)	8 (1.1)	3 (1.1)
Musculoskeletal and Connective Tissue Disorders				
Back pain	6 (2.6)	9 (1.9)	15 (2.2)	4 (1.5)
Arthralgia	6 (2.6)	7 (1.5)	13 (1.9)	0
Musculoskeletal pain	5 (2.2)	2 (0.4)	7 (1.0)	1 (0.4)
Nervous System Disorders				
Headache	4 (1.7)	58 (12.4)	62 (8.9)	27 (9.9)
Psychiatric Disorders				
Insomnia	4 (1.7)	19 (4.1)	23 (3.3)	5 (1.8)
Anxiety	5 (2.2)	5 (1.1)	10 (1.4)	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	8 (3.5)	8 (1.7)	16 (2.3)	3 (1.1)
Skin and Subcutaneous Tissue Disorders				
Rash	2 (0.9)	13 (2.8)	15 (2.2)	2 (0.7)

From Section 2.7.4, Summary of Clinical Safety, Page 68

Abbreviations: HIV+ = human immunodeficiency virus positive; TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity. The TEAEs are presented alphabetically by system organ class, and by descending order of frequency among all Crofelemer-treated subjects within each system organ class.

TEAEs by Intensity

In the HIV+ Integrated Safety population, most TEAEs were mild or moderate in intensity in each treatment group. A total of 29 of the 696 crofelemer subjects (4%) and 10 of the 274 placebo subjects (4%) experienced severe TEAEs (Table 41). All severe TEAEs in the HIV+ Integrated Safety population occurred in only 1 subject each, with the exception of back pain in 3 subjects (Subjects HV101-0072-0031 and HV101-0072-0035; and Subject HV210-024-0251, who had a medical history of sciatica and disk removal), suicide attempt in 2 subjects in the 250 mg daily dose group (Subjects HV101-0003-0021 and HV101-0084-0008), and vomiting in 2 subjects (Subjects HV209-002-1201 and HV210-019-0443). Of the 2 subjects with severe vomiting, Subject HV209-002-1201 also had upper abdominal pain, flatulence, headache and nausea, all of moderate intensity, in addition to severe vomiting on the first day of trial drug administration; the severe vomiting had a duration of 1 day, the subject continued to participate in the trial, and the TEAE was assigned an “unknown” relationship to trial drug. Subject HV210-019-0443 (Crofelemer > 250 mg daily) had severe nausea and vomiting with onset 11 days after the first dose of trial drug and ending 2 days after the drug was withdrawn (total duration of 5 days); the vomiting was possibly related to Crofelemer in the opinion of the investigator.

Severe TEAEs in the HIV+ Integrated Safety population that were considered possibly or probably related to trial drug by the investigator were the following (1 subject each): blood alkaline phosphatase increased (250 mg daily – see previous section for details); night sweats (> 250 mg daily); dyspnea (> 250 mg daily); headache (> 250 mg daily); nausea and vomiting (> 250 mg daily); muscle spasms (> 250 mg daily); abdominal distension and flatulence (> 250 mg daily); abdominal pain (> 250 mg daily); disorientation, dysarthria, and hallucination (> 250 mg daily); vomiting (> 250 mg daily); and fecal incontinence (placebo).

Table 54: All Severe TEAEs (HIV+ Integrated Safety Population)

Preferred Term	Crofelemer 250 mg Daily N = 229 n (%)	Crofelemer >250 mg Daily N = 467 n (%)	All Crofelemer N = 696 n (%)	Placebo N = 274 n (%)
Any Severe TEAEs	13 (5.7)	16 (3.4)	29 (4.2)	10 (3.6)
Back pain	2 (0.9)	1 (0.2)	3 (0.4)	0
Suicide attempt	2 (0.9)	0	2 (0.3)	0
Vomiting	0	2 (0.4)	2 (0.3)	1 (0.4)
Abdominal distension	0	1 (0.2)	1 (0.1)	0
Abdominal pain	0	1 (0.2)	1 (0.1)	0
Anemia	0	1 (0.2)	1 (0.1)	0
Appendicitis	1 (0.4)	0	1 (0.1)	0
Arthralgia	0	1 (0.2)	1 (0.1)	0
Aspartate aminotransferase increased	0	1 (0.2)	1 (0.1)	0
Blood alkaline phosphatase increased	1 (0.4)	0	1 (0.1)	0
Cardiac arrest	1 (0.4)	0	1 (0.1)	0
Cellulitis	1 (0.4)	0	1 (0.1)	0
Chronic obstructive pulmonary disease	0	1 (0.2)	1 (0.1)	0
Dehydration	0	1 (0.2)	1 (0.1)	0
Depression	0	1 (0.2)	1 (0.1)	0
Disorientation	0	1 (0.2)	1 (0.1)	0
Dysarthria	0	1 (0.2)	1 (0.1)	0
Dyspnea	0	1 (0.2)	1 (0.1)	0
Embolic stroke	0	1 (0.2)	1 (0.1)	0
Escherichia sepsis	1 (0.4)	0	1 (0.1)	0
Flatulence	0	1 (0.2)	1 (0.1)	0
Furuncle	1 (0.4)	0	1 (0.1)	0
Gastroenteritis	0	1 (0.2)	1 (0.1)	1 (0.4)
Hallucination	0	1 (0.2)	1 (0.1)	0
Headache	0	1 (0.2)	1 (0.1)	0
Intracardiac thrombus	0	1 (0.2)	1 (0.1)	0
Muscle spasms	0	1 (0.2)	1 (0.1)	0
Musculoskeletal pain	0	1 (0.2)	1 (0.1)	0
Nausea	0	1 (0.2)	1 (0.1)	0
Neck pain	0	1 (0.2)	1 (0.1)	0
Night sweats	0	1 (0.2)	1 (0.1)	0
Pneumocystis jiroveci pneumonia	0	1 (0.2)	1 (0.1)	0
Pneumonia	0	1 (0.2)	1 (0.1)	1 (0.4)
Radius fracture	1 (0.4)	0	1 (0.1)	0
Rectal ulcer	0	1 (0.2)	1 (0.1)	0

Preferred Term	Crofelemer 250 mg Daily N = 229 n (%)	Crofelemer >250 mg Daily N = 467 n (%)	All Crofelemer N = 696 n (%)	Placebo N = 274 n (%)
Renal failure acute	0	1 (0.2)	1 (0.1)	1 (0.4)
Sciatica	1 (0.4)	0	1 (0.1)	0
Skin laceration	0	1 (0.2)	1 (0.1)	0
Suicidal ideation	1 (0.4)	0	1 (0.1)	0
Toothache	1 (0.4)	0	1 (0.1)	0
Tracheobronchitis	1 (0.4)	0	1 (0.1)	0
Alcohol withdrawal syndrome	0	0	0	1 (0.4)
Diffuse large B-cell lymphoma	0	0	0	1 (0.4)
Drug hypersensitivity	0	0	0	1 (0.4)
Ear infection	0	0	0	1 (0.4)
Fecal incontinence	0	0	0	1 (0.4)
Hepatic failure	0	0	0	1 (0.4)
Intracranial aneurysm	0	0	0	1 (0.4)
Phlebitis	0	0	0	1 (0.4)

From HIV+ Table 2.6; corresponding HIV+ Listing 2; Summary of Clinical Safety Page 71
Abbreviations: HIV+ = human immunodeficiency virus positive; TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity.

TEAEs by Relationship to Trial Drug Per Investigator

The incidence of drug-related TEAEs (i.e., as determined by the investigator) in the HIV+ Integrated Safety population was 19% for all crofelemer subjects and 12% for placebo subjects (Table 55). When adjusted for exposure duration (event/PEY), the incidence of drug-related TEAEs was similar between the groups. Drug-related TEAEs reported for ≥ 1% of subjects who received Crofelemer were headache (6%); flatulence, nausea, and insomnia (2% each); and dyspepsia, abdominal pain, pyrexia, dizziness, and rash (1% each). When adjusted for exposure duration (event/PEY), the incidence of drug-related TEAEs was similar between the all Crofelemer and placebo groups.

Table 55: Drug-Related TEAEs Occurring in ≥ 1% of All Crofelemer-Treated Subjects or Placebo Subjects (HIV+ Integrated Safety Population)

System Organ Class Preferred Term	Crofelemer 250 mg Daily N = 229 n (%)	Crofelemer >250 mg Daily N = 467 n (%)	All Crofelemer N = 696 n (%)	Placebo N = 274 n (%)
Any Drug-related TEAEs	27 (11.8)	107 (22.9)	134 (19.3)	34 (12.4)
Gastrointestinal Disorders				
Flatulence	7 (3.1)	6 (1.3)	13 (1.9)	1 (0.4)
Nausea	3 (1.3)	9 (1.9)	12 (1.7)	2 (0.7)
Dyspepsia	3 (1.3)	7 (1.5)	10 (1.4)	1 (0.4)
Abdominal pain	1 (0.4)	8 (1.7)	9 (1.3)	0
General Disorders and Administration Site Conditions				
Pyrexia	0	7 (1.5)	7 (1.0)	1 (0.4)
Nervous System Disorders				
Headache	1 (0.4)	38 (8.1)	39 (5.6)	16 (5.8)
Dizziness	1 (0.4)	6 (1.3)	7 (1.0)	0
Psychiatric Disorders				
Insomnia	0	11 (2.4)	11 (1.6)	4 (1.5)
Skin and Subcutaneous Tissue Disorders				
Rash	1 (0.4)	8 (1.7)	9 (1.3)	1 (0.4)

From Section 2.7.4, Summary of Clinical Safety, Page 72
Abbreviations: HIV+ = human immunodeficiency virus positive; TEAE = treatment-emergent adverse event.
Note: TEAEs are presented alphabetically by system organ class, and by descending order of frequency among all Crofelemer-treated subjects within each system organ class. If a subject experienced more than 1 adverse event, the subject was counted only once for that preferred term or system organ class

7.4.2 Laboratory Findings

Clinical Laboratory Evaluations Overview

Mean changes from baseline in the hematology, blood chemistry, and urinalysis results were small and not clinically notable in any treatment group:

- During the PC phase of the ADVENT trial (combined analysis of Stages 1 and 2).
- In the Long-Term Crofelemer Experience Safety population from the ADVENT trial.

- In the HIV+ Integrated Safety population (ADVENT, 37554-210, and 37554-209 trials).

Individual Clinically Significant Abnormalities

- Treatment-emergent AEs associated with abnormal laboratory values were infrequent during the PC phase of the ADVENT trial. Blood bilirubin increased and blood bilirubin unconjugated increased were the only laboratory results reported as TEAEs in >1% of all Crofelemer or placebo subjects; each of these TEAEs occurred in a higher percentage of placebo subjects and is associated with worsening hepatic function. These events are consistent with the HIV population and occurred in similar proportions of Crofelemer- and placebo-treated subjects. Liver dysfunction is frequently observed in HIV+ individuals due to the high prevalence of concomitant hepatitis B and C infection, alcohol/drug abuse, and ART related hepatotoxicity and other adverse drug reactions in the population (Price, 2010).

- In the ADVENT Long-Term Crofelemer Experience Safety population, the most frequent laboratory results reported as a TEAE in all Crofelemer subjects were ALT increased and AST increased (3% each), and blood bilirubin increased (2%). These TEAEs are related to worsening hepatic function, are consistent with an HIV+ population, and occurred at rates comparable to those observed in the PC phase of the ADVENT trial when adjusted for exposure duration.

- In the HIV+ Integrated Safety population, the most frequent laboratory results reported as TEAEs in all crofelemer subjects were ALT increased, AST increased, and blood bilirubin increased; all of these were reported for 1% of all crofelemer and 1% of placebo subjects. These TEAEs occurred at rates comparable to those observed in the PC phase of the ADVENT trial when adjusted for exposure duration (events/PEY). Moreover, they are related to worsening hepatic function and consistent with an HIV+ population.

7.4.3 Vital Signs

Mean changes from baseline in vital signs (sitting blood pressure, heart rate, respiratory rate, weight, height, body mass index, and temperature) were small and not clinically notable:

- In either Crofelemer or placebo subjects during the PC phase of the ADVENT trial (Stages 1 and 2 combined).

- In either dose group in the ADVENT Long-Term Crofelemer Experience Safety population.

- In any Crofelemer group or the placebo group in the HIV+ Integrated Safety population (Trials ADVENT, 37554-210, and 37554-209).

7.4.4 Electrocardiograms (ECGs)

Cardiac Safety
The cardiac safety of Crofelemer was assessed in nonclinical studies (hERG potassium channel inhibition and dog cardiovascular safety) and clinical trials (ADVENT). The data do not indicate the presence of a significant cardiac safety risk associated with Crofelemer administration.

ECGs in Clinical Trials

(a) ECGs: ADVENT PC Phase Safety Population
There were minimal changes from baseline in ECG parameters for each treatment group during the PC phase of the ADVENT trial. Mean changes were comparable between the placebo and Crofelemer treatment groups; Stages 1 and 2 combined).

Least square mean differences in changes from baseline between Crofelemer and placebo (i.e., placebo-corrected changes from baseline) and 90% confidence intervals (CI) were calculated for the corrected QT interval using Fridericia's correction (QTcF), Bazett's correction (QTcB), and linear regression (QTcL) at Week 4 and end of treatment in the PC phase. Crofelemer treatment resulted in small (< 0.5 msec) placebo corrected changes from baseline in QTcF interval, thereby indicating minimal effects of Crofelemer on QTcF interval duration. Differences between crofelemer and placebo were conserved across methods used for QTc interval correction (i.e., Fridericia, Bazett, or linear regression).

Similar proportions of all Crofelemer subjects (29%) and placebo subjects (26%) had shifts from normal ECG findings at baseline to postbaseline abnormal results. There were no notable differences between Crofelemer and placebo groups in the proportions of subjects who had shifts (increases) in QTc intervals (QTcF, QTcB, or QTcL) from baseline to postbaseline time points. For example, QTcF interval shifts of > 60 msec were experienced by 1 Crofelemer subject (< 1%) and 3 placebo subjects (2%) and QTcF interval shifts of 30 to 60 msec were experienced by 8 Crofelemer subjects (4%) and 3 placebo subjects (2%).

In summary, no ECG signals suggesting a cardiac safety risk were identified in subjects treated with Crofelemer at any dose compared with placebo during the PC phase of the ADVENT trial.

(b) ECG: Long-Term Crofelemer Experience Safety Population - ADVENT

ADVENT PF phase was not uncontrolled. No ECG signals suggesting a cardiac safety risk were identified in Crofelemer-treated patients at any dose.

Cardiac Adverse Events in ADVENT Trial

No subject experienced cardiac AEs during the PC phase of the ADVENT trial. During the PF phase, 3 subjects who received Crofelemer 125 mg bid had cardiac AEs. Each of these subjects had co-morbidities that affect cardiac function such as hypertension, coronary artery disease, hyperlipidemia, chronic obstructive pulmonary disease, or asthma, and other clinically significant co-morbidities, including smoking or alcoholism prior to study entry. In addition, these subjects were receiving medications (ketoconazole, quetiapine, methadone, efavirenz, or ritonavir) that potentially prolong the QTc interval (Takemasa, 2008; Gajwani, 2000; Martell, 2005; Sani, 2005).

Changes of QTc vs. Crofelemer Plasma Concentrations in ADVENT Trial

A population PK sampling design was used for the exploratory characterization of the population pharmacokinetics of Crofelemer. Plasma samples were collected from subjects at Visits 0, 1, 3, and 8 for analysis of Crofelemer concentrations. The data demonstrate that sufficient samples were taken across each subinterval of the dosing regimen to assure appropriate characterization of Crofelemer pharmacokinetics by a population-based approach.

In HIV-infected patients in the ADVENT study, at the dose chosen following Stage 1 of the study (125 mg bid), less than 1% of plasma samples had quantifiable Crofelemer exposure, comparable to results from the Crofelemer 250 mg bid treatment arm. Approximately 15% of samples had quantifiable Crofelemer plasma concentrations at the highest dose administered (500 mg bid). No quantifiable Crofelemer concentrations were detected in plasma samples from subjects receiving placebo. These results are consistent with those observed in other PK studies and support the conclusion that systemic absorption of Crofelemer is negligible in humans following oral administration, consistent with its topical mechanism of action at the GI epithelium.

Statistical analysis was conducted to determine whether a relationship exists between Crofelemer plasma concentrations and changes in QTc interval. Plasma concentration data and associated QTcF data were combined from studies conducted in healthy subjects and patients (CFFE1091 and ADVENT, respectively), for a total of 531 data points. The analysis demonstrated that there is no relationship between change from baseline in QTcF and crofelemer plasma concentration (slope = -0.26 with 95% confidence interval of -0.77 to 0.25). Based on this analysis, no increase in QTcF is anticipated in association with increased Crofelemer plasma concentrations. In addition, this analysis was conducted for QTcB and QTcL. These analyses showed no relationship between change in baseline in QTc by either correction method and Crofelemer plasma concentration.

In Vitro hERG Inhibition

Study AA63535 was conducted to assess the effects of Crofelemer on the hERG potassium ion channel. In the course of 2 experiments, the effect of Crofelemer on hERG tail current was tested at concentrations ranging from 1 nM to 30 µM in human embryonic kidney (HEK)-293 cells stably transfected with hERG (HEK-293/hERG). The results showed that the estimated half-maximal inhibitory concentration (IC50) values for Crofelemer inhibition of hERG tail current were 1.79 µM and 1.75 µM for the first and second set of experiments, respectively. The positive control cisapride (10 µM) inhibited hERG tail current by an average of 99.67% and 100.47% for the first and second set of experiments, respectively, consistent with its known pharmacologic action. In the laboratory that conducted the study, validation experiments demonstrated a cisapride IC50 of 6.44 nM for hERG inhibition.

The mean Crofelemer IC50 for this study, 1.77 µM, is > 135-fold above the highest unbound plasma observed in a human PK study (37554-210-PK) and 1392-fold above the highest unbound plasma concentration observed in the pivotal Phase 3 trial in subjects with HIV-associated diarrhea (ADVENT). These substantial safety margins greatly exceed the 30-fold separation that is commonly associated with minimization of risk of clinical QT interval prolongation (Redfern, 2003).

7.4.5 Special Safety Studies/Clinical Trials

HIV Parameters

(a) ADVENT PC Phase Safety Population
Crofelemer treatment did not adversely affect HIV status in the PC phase of the ADVENT trial; individual subject changes in HIV parameters were comparable in the Crofelemer and placebo treatment groups.

(b) Long-Term Crofelemer Experience Safety Population - ADVENT
In the Long-Term Crofelemer Experience Safety population, potentially clinically significant shifts from baseline to the end of treatment in HIV viral load and CD4 count were infrequent and comparable to the profile observed in the PC phase. In total, 89% of all Crofelemer subjects experienced no notable shift or an increase in viral load from baseline, indicating both adherence to their ART regimen, and continued ART efficacy. Only 2% of all Crofelemer subjects experienced an increase in viral load from < 400 copies/mL (lower limit of quantitation) to > 400 HIV copies/mL. Similarly, 86% of all Crofelemer subjects experienced no notable shifts or a decrease in CD4 count from baseline. Shifts in CD4 count from > 500 cells/mL at baseline to ≤ 500 cells/mL at the end of PC treatment were experienced by 7% of all Crofelemer subjects, comparable to the placebo group in the PC phase.

In summary, the profile of changes in CD4 counts and changes in viral load did not suggest any clinically relevant trends with respect to increases or decreases from

baseline with extended (up to 6 months) Crofelemer treatment. There was no indication that Crofelemer had an adverse impact on HIV status or the efficacy of ART.

No other special safety studies/clinical trials were conducted as part of the Crofelemer development plan.

7.4.6 Immunogenicity

Immunogenicity studies were not part of the Crofelemer development plan.

The absorption of Crofelemer (enteric-coated tablets or beads) was minimal following oral dosing in healthy adults or in human immunodeficiency virus-positive (HIV+) subjects, in either the fasted or fed state. Across all the PK studies, less than 5% of healthy and HIV-associated diarrhea subjects had detectable plasma concentrations of Crofelemer following oral dosing. The high degree of human plasma protein binding (approximately 97%) further limits systemic exposure to Crofelemer. At the therapeutic Crofelemer dose of 125 mg twice daily in the ADVENT, less than 1% of plasma samples had Crofelemer concentrations above the limit of quantification (LOQ).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no evidence of dose dependency for adverse events over the range of doses studied (see Sections 7.3 and 7.4)

7.5.2 Time Dependency for Adverse Events

The placebo-controlled phase of Study ADVENT was a 4-week study. Analysis of time dependency for adverse events was not applicable.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not part of the Crofelemer development plan. In the integrated safety population (N = 696), 54.2% (377/696) patients with Crofelemer treatment were Caucasian, 28.9% (201/696) African American, and 16.1% (112/696) Asian/Pacific Islander, and Hispanic. The overall rates of AEs were low, and exploration of AEs by race or ethnic background was not performed.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not part of the Crofelemer development plan.

7.5.5 Drug-Drug Interactions

The potential interaction of Crofelemer with antiretroviral agents zidovudine, lamivudine, and nelfinavir was investigated. Crofelemer administration had no statistically significant effect on nelfinavir pharmacokinetics. No statistically significant interaction was seen for zidovudine PK parameters except for zidovudine mean T_{max} (time to C_{max}), which increased by 34% with crofelemer administration. In addition, Crofelemer altered the pharmacokinetics of lamivudine including statistically significant decreases in area under the concentration-time curve (AUC) (21%) and C_{max} (19%). None of these PK changes is expected to cause clinically significant changes in the pharmacodynamics of these antiretroviral drugs.

As part of the ADVENT trial, a population PK sampling design was used for the exploratory characterization of the population PK of crofelemer, including the relationships among Crofelemer treatment, Crofelemer plasma concentrations, steady state concentrations of antiretroviral drugs that subjects were taking, and measures of HIV disease status.

Analyses of population pharmacokinetic data for steady-state concentrations of antiretroviral drugs that subjects were taking in Stage 1 of ADVENT (HIV+ subjects) showed no significant interaction between Crofelemer and the antiretroviral compounds at any Crofelemer dose. These data from HIV+ subjects and results of 37554-103 (healthy subjects), which demonstrated minimal effects of Crofelemer coadministration on ART pharmacokinetics, are consistent with the absence of significant effects of Crofelemer on parameters reflecting HIV status (e.g., CD4 counts and viral load), and with the essentially undetectable plasma exposure to Crofelemer at the doses tested in ADVENT.

The profile of changes in CD4 counts and changes in viral load did not suggest any medically relevant trends with respect to increases or decreases from baseline with Crofelemer treatment.
There was no indication that crofelemer had an adverse impact on HIV status or the efficacy of ART.

^{14}C-methylated-Crofelemer, a ^{14}C-methylated analog of Crofelemer, was used in studies of intestinal permeability in Caco-2 cells in vitro, protein binding in vitro, and Crofelemer mass balance/distribution in vivo in rats. Crofelemer is purified from a natural source, and a ^{14}C radiolabel of the molecule cannot be synthesized directly. Results using ^{14}C-methylated Crofelemer may not accurately characterize the intestinal permeability,

protein binding, and distribution of native Crofelemer. Brief conclusions from these studies are provided here.

- The intestinal permeability of 14C-methylated crofelemer and marker compounds using Caco-2 cell monolayers was evaluated. It was concluded that very little (if any) Crofelemer absorption or secretion occurred in this in vitro Caco-2 model. Furthermore, there was no P-glycoprotein-mediated transport of ^{14}C-Crofelemer under the conditions of this study.

- The percent protein binding of 14C-methylated-crofelemer to human plasma proteins was evaluated at concentrations of 30 and 50 µM. The calculated recoveries of the ^{14}Cmethylated Crofelemer at the end of the incubations were approximately 90% for all species studied and across all concentrations. ^{14}C-methylated Crofelemer exhibited 95.4% and 98.8% binding to human plasma proteins at 30 and 50 µM concentrations, respectively.

- The absorption, tissue distribution, and excretion (mass balance) of a single oral dose (approximately 10 µCi/kg) of ^{14}C -methylated Crofelemer (measured by total radioactivity) over 72 hours post-dose were characterized in Sprague-Dawley rats. The results of analyses at 72 hours post dose indicated that the majority of the ^{14}C-methylated Crofelemer remained in the GI tract tissues and was excreted unabsorbed (≈1% of the oral radioactive dose was absorbed as indicated by the urinary levels of radioactivity). These data confirm results from both nonclinical and clinical studies, which indicate that Crofelemer has very low oral bioavailability.

Inhibition of substrate transport by membrane transporters was observed *in vitro*, with Crofelemer IC50 values ranging from 7 to 30 µM; however, no inhibition was observed at physiologically relevant concentrations. In human hepatocytes treated with Crofelemer *in vitro*, no induction of cytochrome P450 (CYP) activity was observed at 10 nM, 100 nM, or 1000 nM Crofelemer and no inhibition was observed at Crofelemer concentrations ranging from 0.3 µM to 300 µM when compared to vehicle controls. Inhibition of CYP activity was evident following incubation of Crofelemer with CYP isoenzymes in microsomes, calculated Crofelemer IC50 values ranged from 0.28 µM for CYP2C8 to 3.5 µM for CYP2C9. These differing results, CYP inhibition by Crofelemer in microsomes and no effect on CYP in hepatocytes exposed to Crofelemer, were likely the result of limited access of Crofelemer to CYP isoenzymes in hepatocytes due to the lack of cellular permeability and the high molecular weight of Crofelemer (i.e., > 2000 g/mol), which would limit passage across the cell membrane of hepatocytes. There is direct exposure of Crofelemer to CYP isoenzymes in microsomes, which are subcellular components without a surrounding cellular membrane.

The lack of Crofelemer effects on CYP metabolism and GI absorption-based interactions (e.g., via interaction with P-gp or other membrane transport proteins)

indicate that there is minimal risk of drug-drug interactions between Crofelemer and other drugs in HIV+ subjects.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of crofelemer.

7.6.2 Human Reproduction and Pregnancy Data

No studies with Crofelemer were conducted in pregnant women.

Animal studies showed no effect to minimal effects on maternal and embryo-fetal development and male or female fertility with at doses as high as 738 mg/kg/day in rats and 200 mg/kg/day in rabbits. In pre- and post-natal development studies in rats, the NOAEL for F_0 maternal toxicity, F_1 parental toxicity, F_1 reproductive toxicity and F_2 developmental toxicity was determined to be 738 mg/kg/day; the NOAEL for F_1 neonatal toxicity was determined to be 369 mg/kg/day.

7.6.3 Pediatrics and Assessment of Effects on Growth

Effects of Crofelemer on pediatric growth were not assessed in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
There has been no reported experience with overdosage of Crofelemer in humans.

Drug Abuse
Due to the mode of action, abuse is not expected. No case of Crofelemer abuse has been reported during the clinical trials for Crofelemer tablets in the treatment of diarrhea in HIV+ individuals, d-IBS, or non-specific diarrhea/travelers' diarrhea.

Withdrawal and Rebound are not expected.

7.7 Additional Submissions / Safety Issues

Additional submissions include the preliminary data of Study CFHD3092 (an ongoing, Phase 3, open-label trial to evaluate the safety and tolerability of Crofelemer in HIV+ individuals) submitted as a 120-day update to the Integrated Summary of Safety (ISS). Also, a QT (TQT) trial in healthy adults, CFQT1092, was recently completed. The analyses of data from trial CFQT1092 are currently in progress.

Safety Results from Integrated Analysis
Enrollment in long-term, open-label, Phase 3 trial CFHD3092 was completed. The 48-week treatment period of this trial is currently ongoing. As of the data cut-off of December 31, 2011 for this 120-day update, 251 subjects were enrolled, 250 subjects received Crofelemer, and 218 subjects are currently ongoing. No subject has completed the 48-week study. No deaths have been reported in CFHD3092, 12 subjects (5%) experienced treatment-emergent SAEs (none were considered related to study medication), and 8 subjects (3%) had TEAEs resulting in discontinuation of trial drug.

Study CFQT1092 was a Phase 1 TQT trial to evaluate the effect of therapeutic and supratherapeutic single-doses of Crofelemer on the QT/corrected QT (QTc) intervals in healthy subjects. The study protocol was designed according the ICH E14 guidance on clinical evaluation of QT/QTc interval prolongation (FDA CDER/CBER guidance for industry, 2005). The primary objective was to evaluate the effect of Crofelemer on cardiac ventricular repolarization, specifically the Fridericia's corrected QT-interval (QTcF) from the surface ECG. The secondary objectives were to evaluate the effect of treatment with Crofelemer on heart rate, PR interval, QRS duration, and waveform composition as seen on the surface ECG. This was a single-center, 4-way, randomized, placebo- and active-controlled, cross-over study. Subjects were randomly assigned to receive each of the following 4 treatments according to a 4 x 4 Williams square cross-over design. There were 7-day wash-out intervals between doses.

- Therapeutic dose (Crofelemer 125 mg)
- Supratherapeutic dose (Crofelemer 1250 mg)
- Moxifloxacin (400 mg)
- Placebo

Subjects had an ambulatory 12-lead monitor (H12+, Mortara Instruments, Milwaukee, WI) with a 30-hour, high-fidelity (1000 Hz) flashcard placed on Day 1, at least 2 hours prior to dosing. Monitoring continued for 24 hours after dosing. The nominal extraction times were predose (-90 minutes, -60 minutes, and -30 minutes relative to dosing), and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours post dose. At each nominal time-point, ECGs were extracted in triplicate. Electrocardiograms were extracted with approximately 1 to 2 minutes between ECGs. Triplicate ECGs were measured using semi-automated methods for the ECG intervals and overall ECG interpretation. Twelve-lead ECGs were performed and transferred to the central ECG laboratory ((b) (4)

(b) (4) for analysis that was blinded to treatment assignment. At the central laboratory, the cardiac technician annotated the Global Superimposed Median beat. The QT interval was measured from the earliest detection of depolarization in any lead to the latest detection of repolarization in any lead. The over-reading cardiologist, who was blinded to treatment assignment, gave a clinical interpretation for each ECG at each time point. Blood samples for pharmacokinetics were obtained after each nominal ECG extraction timepoint.

Phase 1 trial CFQT1092 shows a negative TQT result for Crofelemer. The upper limits of the 95% one-sided confidence intervals (CIs) for the placebo-corrected changes from baseline in QTcF intervals (primary endpoint of the trial) were less than 10 msec at each postdose time point following single doses of Crofelemer 125 mg (therapeutic dose) and crofelemer 1250 mg (supratherapeutic dose). Treatment with the positive control, moxifloxacin, resulted in least square mean placebo-corrected changes from baseline in QTcF interval of 8.8 msec to 13.2 msec from 1.5 to 4 hours post dose, with upper bounds of 95% one-sided CIs of 11.2 to 16.3 msec at these postdose time points. These changes in QTcF intervals following moxifloxacin treatment are consistent with published results from a similar TQT study (Poordad, 2009). (QTcF is the corrected QT interval using Fridericia's formula.)

Preliminary pharmacokinetic data from study CFQT1092 indicate no Crofelemer in plasma samples following placebo treatment, minimal absorption following the therapeutic (125 mg) Crofelemer dose (1 of 22 subjects had detectable plasma Crofelemer concentrations, C_{max} = 57.2 ng/mL at approximately 6 hours post dose), and higher Crofelemer plasma concentrations following the supratherapeutic (1250 mg) Crofelemer dose (17 of 22 subjects had detectable plasma Crofelemer concentrations, mean Cmax = 174 ng/mL, median Tmax approximately 6 hours post dose).

The safety profile from the HIV+ Integrated Safety population, which included subjects from the CFHD3092, ADVENT, 37554-210, and 37554-209 trials (n = 1176), supports the findings from the ADVENT trial alone. Review of the integrated population showed no remarkable differences between the Crofelemer and placebo groups in the incidence of TEAEs, drug-related TEAEs, severe TEAEs, treatment-emergent SAEs, and TEAEs resulting in trial drug discontinuation when the data were normalized for exposure duration.

Duration of exposure to Crofelemer, at the time of data cut-off for this 120-day update, was ≥ 6 months for 273 subjects and ≥ 12 months for 25 subjects in the long-term experience pool, which included HIV+ subjects with diarrhea in ADVENT and ongoing trial CFHD3092 (there are 218 subjects who are currently receiving 125 Crofelemer bid in the 48-week trial CFHD3092). Median duration of exposure to Crofelemer was 170 days (range, 10 to 420 days) in the ADVENT and CFHD3092 pool.

Notably, the incidence of constipation was low in all Crofelemer-treated and placebo-treated subjects (2% Crofelemer versus 1% placebo; mean duration of exposure was 5-fold longer in the all Crofelemer group compared to placebo). This is considerably lower than the 5% incidence of constipation with loperamide in patients with chronic diarrhea (Imodium package insert). No case of constipation in Crofelemer-treated subjects was considered an SAE.

8 Postmarket Experience

Crofelemer has not been marketed in any region to date. "Dragon Blood" is the dietary supplement version of Crofelemer. According to Drug.com issued by NCI, NIH, there has been no major toxicities reported with the use of "Dragon Blood".

9 Appendices

9.1 Literature Review/References

Literature Review

Literature review focuses on (1) searching confounding factors that may cause spontaneous recovery of diarrhea (false negative); and (2) identifying the unmet medical needs of anti-HIV diarrhea agents in the field of HIV/AIDS therapy.

(1) Confounding factors:

- Opportunistic infection diarrhea may spontaneously recover or improve. To exclude infectious diarrhea from the study, repeated stool testing, stool culture, and intestinal biopsy are required (Wilcox, 1996; Kartalija, 1999; Simon, 1993; Call, 2000).
- The possibility of infectious diarrhea increases when CD4 cell counts of HIV patients fall below 200 cells/mm^3 (Call, 2000).
- Spontaneous recovery of infectious diarrhea may occur when HIV patients are taking ART (Kartalija, 1999).
- ART may inhibit the replication of HIV virion at the intestinal mucosa, and may improve HIV entropathy diarrhea (Kotler, 2005).

(2) Unmet medical needs:

- Gastrointestinal adverse reactions (diarrhea and vomiting) are the leading cause of ART discontinuation (Hawkins, 2010)
- Treating diarrhea improves adherence to ART containing protease-inhibitors (Duran, 2001)
- A systematic study (Nwachukwu, 2008) of clinical trials of HIV diarrhea treatment based on information gathered from the World Health Organization, the CDC, pharmaceutical companies, and experts in the field, and literature search (with the criteria: randomized controlled trials comparing an anti-motility agent or an adsorbent in HIV patients with diarrhea of ≥ 3 weeks duration) showed the following:
    - The current anti-motility class of anti-diarrhea agents including opioid agents do not have appreciable long-term effect against chronic diarrhea (Nwachukwu, 2008);
    - To date, only one study of an adsorbent (attapulgite) was reported. In this single study, no difference was noted in the active treatment arm over the placebo (Nwachukwu, 2008).

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9.2 Additional Information of Individual Studies

Appendix 1: Additional Information for Study ADVENT

Efficacy and Safety Measurements Assessed and Flow Chart

Table 1 summarizes the visits and assessments performed during both Stage 1 and Stage 2 of Study ADVENT. All study visits and procedures performed in Stage 1 and

Stage 2 of the trial were identical. Both stages consisted of a 10 (± 4)-day, single-blind, placebo screening phase; randomization and a 31-day, double-blind, PC phase; and a subsequent 20-week PF extension phase. Subjects participated in either Stage 1 or Stage 2 of the study (i.e., subjects were not allowed to participate in both study stages).

Table 1: Schedule of Study Assessments

	Screening/ Baseline	Placebo-Controlled Treatment Phase			Placebo-Free Extension Phase					14-Day Follow-Up
Visit(s)	**Visit 0** Screening Visit	**Visit 1** Randomization Visit	**Visit 2**	**Visit 3** EPT	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8** EOT	**Telephone call**
Day(s)	Day -13 to -4 + 4 (3)	Day -4 (4) (5)	Day 14 ± 2	Day 29 + 3 (6) (7)	Day 57 ± 4	Day 87 ±4	Day 113 ±4	Day 141 ± 4	Day 169 ± 4 (9)	Day 183 ± 3
Demographics	•									
Medical/Surgical History	•									
HIV Disease History	•									
Medication History	•									
Eligibility Criteria (Inc/Excl)	•									
Randomization		•		• (8)						
Vital Signs	•	•	•	•	•	•	•	•	•	
Physical Exam	•			•					•	
Concomitant Medications		•	•	•	•	•	•	•	•	•
Adverse Events		•	•	•	•	•	•	•	•	•
Compliance Check (Study Drug, IVRS)		•	•	•	•	•	•	•	•	
Study Drug Dispensing/Return	•	•	•	•	•	•	•	•	•	
Chemistry – Comprehensive metabolic panel	•	•	•	•	•	•	•	•	•	
Hematology /Coagulation	•		•	•	•				•	
Plasma for PK sampling	•	•		•					•	
CD4 count, CD8 count	•	•		•	•		•		•	
HIV titer	•	•		•					•	
Urinalysis	•		•	•	•				•	
Stool Sample (1)	•			•	•*	•*	•*	•*	•*	
Pregnancy Test, serum (if applicable)	•			•					•	
Urine drug screen for opiates	•									
12-lead ECG	•			•					•	
PRO Assessments (2)	•			•					•	

From Table 5, Clinical Study Report. Page 54. Abbreviations: IVRS = interactive voice response system; PK = pharmacokinetic; HIV = human immunodeficiency virus; ECG = electrocardiogram; PRO = patient reported outcome; EOT = end of treatment; AE = adverse event; and EPT = End placebo-controlled treatment phase.
(1) Sample collection could have been delayed up to 2 days if a sample could not be produced at the visit; (1.*) stool sample for ongoing watery/loose BM. (2) PRO assessments should be performed **before** all other study-related procedures scheduled for that visit. (3) IVRS, intake of study medications, and discontinuation of ADM begin the day following Visit 0. (4) Visit 1 should occur 10 + 4 days from Visit 0. Use of study medication and recording of IVRS diary entries should continue through these days of extended screening. (5) The first 3-days of double-blind treatment = run-in (Days -3 to -1); subsequent 4 weeks (Days 1 to 28) = efficacy assessment period. Visit 3 is to occur the following day on Day 29. If the screening phase is extended or contracted for whatever reason, Visit 1 will remain Day -4 on the schedule of assessments. (6) Subjects who discontinue prior to the completion of the placebo-controlled treatment phase should undergo Visit 3 (ERT) followed 14 days later by post-dosing telephone call for assessment of adverse events (AEs). (7) Visit 3 may not occur earlier than Day 29, i.e., earlier than 32 days from Visit 1 (*see footnote 5*). (8) Re-randomization of placebo-treated subjects only for extension phase. (9) Subjects who prematurely discontinue therapy during the placebo-free extension phase are to perform Visit 8 (EOT), followed 14 days later by a post-dosing telephone call for assessment of adverse events (AEs).

Study Diary-Interactive Voice Response System (IVRS)

Efficacy assessments were performed using subject diaries, which were entered daily into the IVRS. The subject diaries captured diarrhea symptoms (stool consistency, stool frequency, sense of urgency, fecal incontinence, and abdominal pain or discomfort),

adherence to study medication and ART, and use of ADM or prohibited medications. The information collected from these diaries was used to assess treatment outcomes for the study.

The following information was captured on a daily basis via IVRS throughout the trial:

(a) Date
(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)

The following information was captured throughout the baseline and PC phase (but not the PF extension phase):

(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)

Study Diary (IVRS) Definitions

The following diary definitions were provided to subjects to standardize assessments when using the IVRS:

- Diarrhea was defined as frequent loose or watery bowel movements.

- Bowel movement was defined as a trip to the bathroom with evacuation of stool; number of bowel movements meant the number of trips to the bathroom with evacuation of stool.
  Types of bowel movements were defined as follows:
  - Watery bowel movement was defined as stool that can be poured;
  - Loose bowel movement was defined as soft blobs with no shape or form;
  - Formed bowel movement was defined as a stool like a soft sausage;
  - Hard bowel movement was defined as a stool like a hard or lumpy sausage; and
  - Very hard bowel movement was defined as hard lumps or nuts that are hard to pass.
- Urgency was defined as having to rush to the bathroom for a bowel movement.
- Fecal incontinence was defined as leaking or passing stool at unwanted times (two teaspoons or more of stool).
- Abdominal pain or discomfort was defined as pain, cramping, or bloating that was uncomfortable and/or interrupted normal activities.

Inclusion Criteria
All of the following criteria were required for the inclusion of a patient into the study:

1. Written informed consent

2. Male or female, age ≥ 18 years

3. History of HIV-1 infection confirmed by standard serological tests (positive enzyme-linked immunosorbent assay (ELISA) and Western blot), and/or positive HIV titer confirmed by polymerase chain reaction (PCR) based HIV-1 viral load assay. [Note: documentation of prior and/or current HIV-1 infection must either have been provided, or the subject must have tested positive for HIV-infection at Screening.]

4. Stable antiretroviral therapeutic regimen (no additions, deletions, or changes in type or dose of medication) for treatment of HIV disease and associated conditions (including prophylactic antibiotics for PCP or infection) for at least 4 weeks prior to screening, plus ability to remain on this regimen during the screening and baseline periods and throughout the PC treatment phase

5. Patient-reported history of diarrhea, defined as either persistently loose stools despite regular ADM use, or one or more watery bowel movements per day without regular ADM use, of at least 1 month duration, and for the month prior to screening.

6. Females of child-bearing potential:
Negative pregnancy test within 72 hours prior to receiving the first dose of study medication

7. Sexually active males and females of child-bearing potential:
Agreement to use a method of contraception throughout the study that was deemed acceptable by the investigator.

8. Colonoscopy for colon cancer screening or any other condition within the past 5 years if ≥ 50 years of age. This examination must have demonstrated no evidence of colitis, infection, or neoplasm, with the exception of benign polyps of the colon.

9. Willingness to withdraw all ADM(s) for the first 6 or more weeks of the study (Screening phase and PC treatment phase)

10. Willingness to avoid all prohibited medications for the first 6 or more weeks of the study (Screening period and PC treatment phase)

11. Willingness to comply with the requirements of the study, including regular study visits and IVRS entry

Additionally, to be eligible for inclusion into the PC phase and continued participation in this study, patients reported 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, and urgency on at least 1 of these 7 days.

Exclusion Criteria
Patients were screen failures and were not enrolled into the study if they met any of the following criteria:

1. Pregnancy or breast-feeding

2. Immediate need for GI surgery or intervention for active GI bleeding, peritonitis, intestinal obstruction, or intra-abdominal abscess

3. History of gastric, small-intestinal, or colonic surgery, excluding appendectomy

4. Symptoms of bowel obstruction or confirmed evidence of a stricture

5. Use of opioid pain medication within 2 weeks of screening
   [Subjects receiving the following opiate regimens and therapies were *not* excluded from enrollment if taken within 2 weeks of screening: 1) stable methadone buprenorphine, or buprenorphine/naloxone treatment (no addition, deletion, or change in dose of medication) for the purpose of pain management or addiction management for at least 3 months prior to screening plus the ability to remain on this dose throughout the PC phase; 2) fentanyl transdermal patch therapy for pain management, on a stable dose for at least 4 weeks prior to screening plus the ability to remain on this dose throughout the PC phase; and 3)

opioids used *exclusively* for control of diarrhea– loperamide (Imodium®), diphenoxylate (Lomotil®), codeine, paregoric, or tincture of opium. However, because these are acting as ADM, these drugs must have been stopped on the day following screening.]

6. Positive urine test for opiates, unless the subject was taking an opioid or known to be on stable methadone, buprenorphine, buprenorphine/naloxone, or fentanyl transdermal patch therapy, or an opiate-based ADM as defined in Exclusion Criterion 5, and this opioid was identified on the drug screen.

7. Use of an antibiotic within 2 weeks prior to screening, with the exception of stable antibiotic therapy for prophylactic treatment of infection or an HIV-associated condition for at least 4 weeks prior to screening

8. CD4 counts < 100 cells/mm^3

9. Oral temperature greater than 38.0 ^oC, or unintentional weight loss of 5.0 kg or greater during the prior 2 months

10. Positive GI biopsy, GI culture, or stool test result in the past 4 months for any of the following:

Bacteria: - *Salmonella spec.*
- *Shigella spec.*
- *Campylobacter spec.*
- *Yersinia spec.*
- *Mycobacterium spec.*

Bacterial toxin: -*Clostridium difficile*

Ova and parasites: - *Giardia spec.*
- *Entamoeba spec.*
- *Isospora spec.*
- *Cyclospora spec*
- *Cryptosporidium spec.*
- *Microsporidium spec.*

Viruses: - *Cytomegalovirus spec.*

Or any fecal pathogen requiring antibiotic treatment within 14 days of screening

11. Evidence on prior colonoscopy or upper endoscopy of colitis, enteritis, infection (HIV associated or otherwise), or neoplasm, other than benign polyps.

12. Positive occult blood or lactoferrin (qualitative) on stool sample, unless colonoscopy within the past 4 months had demonstrated no evidence of colitis, neoplasm, or infection. [Subjects were able to re-screen if no evidence of these abnormalities was

detected on a subsequent colonoscopy and re-screening occurred within 4 months from the date of the examination.]

13. Bright red blood per rectum judged not to be of an anal (hemorrhoid, fissure) origin.

14. Any of the following laboratory abnormalities:
- Serum creatinine ≥ 3.0 mg/dL
- Alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥ 3 x the upper limit of normal [For subjects taking atazanavir or indinavir, which can cause asymptomatic indirect hyperbilirubinemia, the exclusion for total bilirubin was ≥ 5 x the upper limit of normal.]
- Hemoglobin (Hgb) < 8.0 g/dL
- Absolute neutrophil count or lymphocyte count ≤ 500 cells/μL

15. Presence or history of cancer of any type (except treated basal cell carcinoma), including Kaposi's sarcoma or other HIV-associated neoplasm, within the last 5 years

16. History of ulcerative colitis, Crohn's disease, celiac sprue (gluten-enteropathy), chronic pancreatitis, malabsorption, or any other GI disease associated with diarrhea. [Note: Irritable bowel syndrome was not excluded if the diarrhea was judged to result from HIV disease or its treatment. Lactose intolerance treated with lactase supplements or a lactose-free diet was also not excluded if these regimens were maintained during the study.]

17. Use of any investigational drug, with the exception of a drug administered through an expanded access program that was registered with the US FDA, within 4 weeks or 5 halflives (whichever was longer) prior to receiving the first dose of study medication.

18. Nasogastric, gastrostomy, or jejunostomy tube feedings

19. Active drug or alcohol abuse that in the opinion of the investigator could have interfered with the subject's ability to comply with the study protocol.

20. Clinically important co-morbid conditions, including untreated psychiatric disorders, as determined by the investigator, that had the potential to interfere with the subject's ability to comply with the study protocol, place the subjects at increased risk, or interfere with the evaluation of the results.

21. Planned in-patient hospitalization during the trial

Previous randomization into this study, or into any other study in which Crofelemer (i.e., Provir®, SP-303) was administered. [Note: Subjects participating in protocol NP003 (feasibility study) were not excluded, as no study drug was administered.]

Withdrawal Criteria

Investigators were required to withdraw subjects from further study participation under the following circumstances:

1. Withdrawal of consent:
   Subject participation was terminated immediately upon his or her request. Every subject had the right to refuse further participation in the study at any time without providing reasons. However, in such cases the investigator was to obtain the reason if possible and record on the subject CRF.

2. Pregnancy

3. Major GI surgery

4. Use of another investigational drug, with the exception of a drug administered through an expanded access program that was registered with the US FDA, within 4 weeks or 5 half-lives (whichever is longer) prior to receiving the first dose of study medication

A subject may have been withdrawn from further study participation under the following circumstances:

5. Clinically significant exacerbation of diarrhea, defined as 1) an increase of ≥ 8 bowel movements per day, or an absolute number of bowel movements ≥ 12 bowel movements per day, for 3 or more consecutive days; or 2) need for IV hydration or electrolyte replacement; or 3) necessity, in the opinion of the investigator, for treatment with a prohibited ADM.

6. Clinically significant laboratory abnormality or serious / severe AE

7. Repeated use of ADM or opiate pain medications that might have indicated to the investigator that the subject's diarrhea or pain was not adequately controlled

8. Non-attendance of study visits: Non-attendance at 2 consecutive scheduled visits without a reason agreed on by the investigator and sponsor

9. Non-compliance with all required doses of study medication for more than 3 consecutive days; non-compliance greater than 20% of required doses in a given treatment period; or any unauthorized use of study medication

10. Non-compliance with IVRS diary entries for more than 3 consecutive days during the PC treatment phase after at least two attempts by the study site to enforce compliance with diary entry

11. At the discretion of the investigator

Pharmacokinetic Assessments

Table 2 presents the schedule of events for the pharmacokinetic assessments. All randomized subjects in the study were planned for inclusion in the pharmacokinetic study assessments. Blood samples were collected at Visit 0 to obtain baseline viral load, CD4 counts, and concentrations of ART medications. Blood samples were also collected on Visits 1, 3, 4, 6, and 8 for the determination of Crofelemer concentrations, viral load, CD4 counts, and concentrations of ART medications.

Table 2: Schedule of Pharmacokinetic Sampling

	Screening/ Baseline	Placebo-controlled Treatment Phase			Placebo-Free Extension Phase				
Visit(s)	visit 0 screening visit	visit 1 randomization visit	visit 2	visit 3 EPT	visit 4	visit 5	visit 6	visit 7	visit 8 EOT
Day(s)	-14 to -7	-4	14 ± 2	29 + 6	57 ± 4	87 ± 4	113 ± 4	141 ± 4	169 ± 4
Crofelemer		Pre-dose		Pre-dose					Pre-dose
Others	B C	Pre-dose A B C		Pre-dose A B C					Pre-dose

Note:
[a]PK sample for antiviral drugs used in the treatment of HIV

[b]Samples for CD4 and CD8 counts and [c]PCR based HIV-1 viral load assay

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Sensitivity Analyses of ADVENT

Three sensitivity analyses were conducted on the primary endpoint by the Applicant. The first addressed the impact of major protocol deviations on the primary endpoint by analyzing clinical response using the PP population with the methods of Posch and Bauer (Posch, 2005). The second addressed the impact of statistical testing methodology on the primary endpoint. The third controlled for the impact of geographic region on the analysis.

Results for the PP population analysis are presented in Section 6.1.4 in a side-by-side comparison with the primary endpoint using the ITT population. Results for the PP population were consistent with results for the ITT population and supportive of the primary finding. In the PP population, clinical response was experienced by a higher proportion of patients in the Crofelemer 125 mg bid group compared with the placebo group (18% vs. 8%, 1-sided p = 0.0117).

The primary endpoint was also analyzed using a nonparametric test adjusting for stage in the ITT population. In this sensitivity analysis, a consistent and statistically significant Crofelemer treatment effect was also observed (18% vs. 8%).

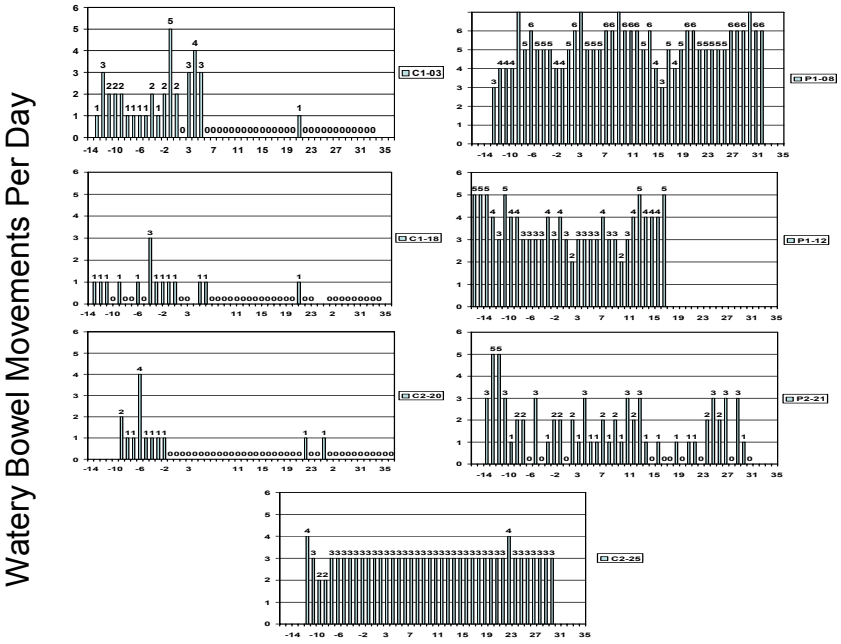
Finally, the primary endpoint was analyzed by geographic region in order to evaluate the consistency of response across the investigative sites. In this sensitivity analysis with geographic region as the strata, clinical response was experienced by a larger proportion of patients in the Crofelemer 125 mg bid group compared with the placebo group (18% vs. 8%).

In summary, results from each of these analyses were consistent with the primary analysis and demonstrated the favorable primary efficacy finding.

Division of Scientific Investigations (DSI) Inspection

DSI medical reviewer, Dr. Khairy Malek, faxed the primary IVRS data of Study Site #45 on April 19, 2012. The reviewer plotted the primary data (Daily watery bowel movements vs. time in PC Phase) in Figure 1. It appears that the number of clinical responder is consistent with the original NDA report: There were 3/4 (75%) patients that received 125 mg Crofelemer during the PC Phase had achieved clinical response (Patients' IDs: C1-03, C1-18, and C2-20). Patient (ID C2-25) was a non-responder.

Figure 1: Clinical responders and non-responder at Study Site #45



From DSI inspection of the primary data: C1-03, C1-18, C2-20: Patients receiving 125 mg Crofeclemer at the placebo-controlled phase of Stage 1 (C1-03, C1-18) or Stage 2 (C2-20, C2-25), respectively (ADVENT); P1-08, P1-12, P2-21: Patients receiving placebo at Stage 1 (P1-08, P1-12) or Stage 2 (P2-21), respectively.

Appedix 2: Study 37554-210

Title: A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Orally Administered SP-303 (Crofelemer) for the Treatment of Diarrhea in Acquired Immunodeficiency Syndrome (AIDS) Patients. (March 25, 1998 to September 27, 1998)

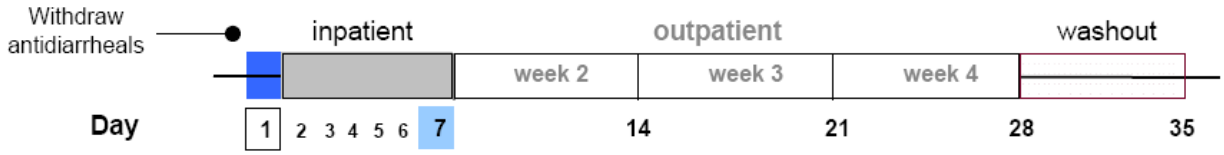
Study Design and Objectives: Study 37554-210 was a Phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial designed to assess the efficacy, safety, and pharmacokinetics of 3 doses of Crofelemer in patients with HIV-associated diarrhea.

The primary objective of the trial was to demonstrate the efficacy of Crofelemer for decreasing stool weight (primary efficacy endpoint) in HIV/AIDS patients with diarrhea over 6 days of treatment. The primary endpoint of reduction in stool weight is an appropriate measure of the extent of watery diarrhea in patients with HIV-associated diarrhea due to high water content in the diarrhea experienced by these patients.

The secondary objective of the study was to evaluate Crofelemer's safety, durability of response, and efficacy in other endpoints over 28 days of treatment. There were 3 assessment periods during the study (Figure 2): a 24-hour screening period to ensure that the subjects met all of the study criteria, during which baseline stool weight was assessed (Day 1); a 6-day inpatient treatment period (Days 2-7); and a 21-day outpatient treatment period (Days 8-28) plus a 7-day withdrawal period (Days 29-35). For the in-patient treatment period, patients were randomly assigned to 1 of 4 treatment groups at a ratio of 1:1:1:1 (approximately 80 patients per treatment group):

- Crofelemer 500 mg beads 4 times daily (qid)
- Crofelemer 500 mg tablets qid
- Crofelemer 250 mg tablets qid
- Placebo qid

Figure 2: Study 37554-210 Assessment Periods



Patients who were determined to be "responders" (defined as having >50% decrease in stool weight from baseline to Day 7 and at least a partial improvement in 2 or more of the Day 7 overall assessments compared to baseline) were entered into the out-patient period (Days 8-28) followed by a 7-day withdrawal phase, with measurements of selected safety and efficacy variables continuing until Day 35. Patients receiving placebo, Crofelemer 250 mg tablets, and 500 mg tablets during the in-patient treatment period continued on these therapies throughout the out-patient period. Patients receiving Crofelemer 500 mg beads were switched to 500 mg tablets during the out-patient period. Non-responders were discontinued on Day 7.

Subject Population: Eligible patients were males or females 18 years or older with confirmed HIV infection that met the CDC criteria for AIDS, were on a stable medical regimen for AIDS, and had a history of diarrhea for ≥14 days. Patients who met the initial eligibility criteria were admitted to the clinical research unit on Day 1 and screening procedures (including assessments of stool frequency, weight, and consistency) were performed. All patients discontinued ADM at least 24 hours prior to screening. Patients who satisfied the entrance criteria and were eligible based on the screening tests (including total stool weight ≥300 grams during the 24-hour screening period) were enrolled in the study.

Efficacy Endpoints: Efficacy measurements included assessments of stool weight and frequency, Daily Gastrointestinal symptom scores (DGIS), measure of relief scores (MORE), and number of early dropouts (prior to completion of 4 days of treatment).

Efficacy endpoints in this trial were as follows:
Primary:

- Change from baseline in daily stool weight during the in-patient period.

Secondary:

- Change from baseline in daily stool frequency during the in-patient period.
- Early dropouts (number of subjects who discontinued prior to completion of 4 days of treatment) due to worsening diarrhea, AEs, or personal reasons.

Additional secondary efficacy endpoints during the in-patient period:

- Change from baseline in DGIS during the Inpatient Period. The DGIS was the daily sum of mean symptom scores for each of 7 symptoms (nausea, vomiting, abdominal pain and/or cramps, excess gas, urgency, tenesmus, and

incontinence) scored 4 times per day. Symptoms were rated on a 4-point scale from 0 = absent to 3 = severe. The DGIS ranged from 0 to 21.

- Measure of relief scores, where MORE was the maximum time with no abnormal stool following the first dose of study drug during the Inpatient Period.
- Relief (free of abnormal stools) for 24 hours or more.
- No watery stools ≥ 2 days during Days 5 - 7 for subjects with urgency and watery stools at baselin.
- No watery stools ≥ 2 days during Days 2 - 7 for subjects with urgency and watery stools at baseline.
- No watery stools on Day 7 for subjects with urgency and watery stools at baseline.

Efficacy Analysis: Efficacy analyses were performed using the ITT population, defined as subjects who received ≥ 1 dose of study drug.

Primary Efficacy Analysis: Daily stool weight at baseline was defined as total daily stool weight on Day 1 (Screening). The primary efficacy endpoint, change from baseline in daily stool weight.

Efficacy Results
Primary efficacy endpoint:
There were significantly greater decreases in stool weight from baseline (Day 1) to Day 7 (last inpatient day) in the 500 mg tablets group (500 mg tablet qid) compared with placebo (p = 0.0107) in the ITT population. Mean (± SD) change from baseline to Day 7 in stool weight was -420.1 (± 894.38) g in the 500 mg tablets group and -332.0 (± 439.97) g in the placebo group.

Secondary efficacy endpoints:

- Significantly greater decreases in stool frequency from baseline (Day 1) to Day 7 were observed in the 500 mg tablet group compared with placebo (p = 0.0254) in the ITT population. Also, greater decreases in stool frequency from baseline to Day 5 and Day 6 were experienced by subjects in the 500 mg tablet group compared with placebo. The decreases (improvements) in DGIS scores from baseline (Day 1) to Day 7 were significantly greater in the 500 mg tablet group compared with placebo (p = 0.0002) in the ITT population. Also, decreases from baseline (improvements) in DGIS score were significantly greater in the 500 mg tablet group at Day 4, Day 5, and Day 6 compared with placebo (p = 0.0154, p = 0.0017, and p = 0.0033, respectively).
- Significant efficacy was also observed in a longitudinal, repeated measure analysis of data over the course of the Inpatient Period (Days 2-7); p = 0.0113 for changes in total stool weight, p = 0.0229 for changes in stool frequency, and p = 0.0043 for changes in DGIS scores in favor of the 500 mg tablets group when compared with placebo.

The anti-diarrheal responses to Crofelemer treatment were shown higher in subgroups of subjects with severe diarrhea (stool weight > 1000 g versus ≤ 1000 g), high stool frequency (> 5/day versus ≤ 5/day), or high DGIS score (> 3 versus ≤ 3) at baseline.

Supplementary Endpoints:
Treatment with Crofelemer 500 mg tablets qid resulted in significantly greater frequencies of subjects, when compared with placebo, who achieved the following endpoints (ITT population):

- No watery stools for ≥ 2 days during Days 5 - 7 (p = 0.0200 by Chi-square test).
- No watery stools for ≥ 2 days during Days 2 through 7 (p = 0.0092 by Chi-square test).
- No watery stools on Day 7 (p = 0.0145 by Chi-square test).

Statistically significant positive effects of treatment with Crofelemer 500 mg beads were also observed for these same respective endpoints when compared with placebo (p ≤ 0.0052).

Appendix 3: Study 37554-209

Title: Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Assess the Safety and Efficacy of Orally Administered SP-303 (Crofelemer) for the Symptomatic Treatment of Diarrhea in Acquired Immunodeficiency Syndrome (AIDS) Patients (April 7, 1997 to September 26, 1997)

Study Design and Objectives: Study 37554-209 was a Phase 2, randomized, double-blind, multicenter (2 sites), placebo-controlled, parallel-group trial designed to assess the efficacy and safety of Crofelemer 500 mg beads in subjects with HIV-associated diarrhea.

The primary objectives of 37554-209 were to evaluate the safety and efficacy of orally administered Crofelemer for 96 hours for the symptomatic treatment of diarrhea in AIDS patients. The secondary objectives were: 1) to characterize stool chloride ion concentration and daily stool chloride output in AIDS patients with diarrhea; 2) to compare stool chloride ion concentration and daily stool chloride output in AIDS patients with diarrhea treated with Crofelemer or placebo; and 3) to assess stool consistency in AIDS patients with diarrhea treated with Crofelemer or placebo.

There were 3 assessment periods during the study: 1) a 24-hour in-patient screening period to ensure that the subjects met all of the study criteria, during which baseline stool weight was assessed; 2) a 4-day inpatient treatment period, during which all patients received their assigned treatment 4 times per day (Days 1-4); patients were

discharged from the hospital after 96 hours of treatment if clinically stable); and 3) a follow-up visit 7-9 days after discharge from the hospital. The use of ADM was not allowed during the study.

Subject Population: Patients were 18 to 60 years of age, had HIV infection, met CDC criteria for AIDS, were on a stable medical regimen for AIDS, and had abnormal stool weight > 200 grams and ≥ 3 abnormal stools during the 24-hour Screening Period.

Efficacy Endpoints: Efficacy measurements included assessments of stool weight and frequency, abnormal stool frequency, DGIS, MORE, and stool chloride concentration. Efficacy endpoints in this study were as follows:
Primary:

- Change from baseline in daily stool weight during the Treatment Period.

Secondary:

- Change from baseline in daily abnormal stool frequency, defined as watery or soft stool, during the Treatment Period.
- Change from baseline in daily stool frequency during the Treatment Period.
- Change from baseline in DGIS during the Treatment Period. The DGIS was the daily sum of mean symptom scores for each of 7 symptoms (nausea, vomiting, abdominal pain and/or cramps, excess gas, urgency, tenesmus, and incontinence) scored 4 times per day. Symptoms were rated on a 4-point scale from 0=absent to 3=severe. The DGIS ranged from 0 to 21.
- Change from baseline in daily stool Cl^- concentration (mg Cl^-/g stool weight) during the treatment period.
- Measure of relief scores, where MORE was the maximum time with no abnormal stool following the first dose of trial drug during the treatment period.

Efficacy Analysis: Efficacy analyses were performed using the ITT population, defined as subjects who received ≥ 1 dose of study drug.

Primary Efficacy Analyses: Daily stool weight at baseline was defined as total daily stool weight on Day 0 (Screening). The primary efficacy endpoint was change from baseline in daily stool weight.

Efficacy Results
Primary efficacy endpoint: There were significantly greater decreases in stool weight from baseline to Day 4 (last treatment day) in the Crofelemer group compared with placebo (primary efficacy endpoint, p = 0.0335) in the ITT population. Mean (± SD) change from baseline to Day 4 in stool weight was -401.3 (± 531.65) g in the 500 mg beads group and -192.4 (± 381.57) g in the placebo group.

Secondary efficacy endpoints:

- Significantly greater decreases in abnormal (loose and watery) stool frequency and total stool frequency from baseline to Day 4 (last treatment day) were observed in the Crofelemer group compared with placebo ($p = 0.0069$ for abnormal stool frequency and $p = 0.0046$ for total stool frequency) in the ITT population. Also, the Crofelemer group had significantly greater decreases in total stool frequency from baseline to Day 2 ($p = 0.0223$) and from baseline to Day 3 ($p = 0.0140$) compared with placebo.
- Significant efficacy was also observed in a longitudinal, repeated measure analysis of data over the course of the inpatient Treatment Period (Days 1-4); $p = 0.0330$ for changes in abnormal stool frequency, and $p = 0.0236$ for changes in stool frequency in favor of the Crofelemer group when compared with placebo.
- There were significantly greater reductions in stool chloride concentrations in the Crofelemer group when compared with the placebo group ($p = 0.0024$) among ITT subjects with stool chloride data (placebo n=25, Crofelemer n=26). This result is consistent with the known mechanism of action of Crofelemer; inhibition of gastrointestinal CFTR and CACC resulting in inhibition of chloride secretion and accompanying high volume water loss.

The anti-diarrheal responses to Crofelemer treatment were higher in subgroups of subjects with severe diarrhea (stool weight > 740 g versus ≤ 740 g), high abnormal stool frequency (> 5/day versus ≤ 5/day), or high total stool frequency (> 5/day versus ≤ 5/day) at baseline.

Medical Officer Comments:
(1) Studies 37554-210 and 37554-209 are considered to be supportive to ADVENT trial in efficacy assessment. These studies measured daily stool weight in the inpatient period. The results showed that the decreases from baseline in daily stool weight were statistically greater in the 500 mg tablet group as compared with the placebo. The decreases are consistent with the results of ADVENT, and are clinically relevant.

(2) The formulation of Crofelemer in Studies 37544-210 and 37544-209 was different from that of Study ADVENT. There is no data to compare the 500 mg tablets in these studies with the 125 mg in Study ADVENT.

9.3 Labeling Recommendations

Labeling underwent extensive negotiations between the Applicant and FDA. See the final negotiated labeling.

9.4 Advisory Committee Meeting

No advisory committee meeting of Crofelemer was conducted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEN-YI GAO
10/03/2012

ANIL K RAJPAL
10/03/2012
I concur with Dr. Gao.