CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 28, 2012
From	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 202-292
Applicant	Salix Pharmaceuticals, Inc.
Date of Submission	December 5, 2011
PDUFA Goal Date	September 5, 2012 (Priority; includes 3-month extension for a major amendment)
Proprietary Name / Established (USAN) names	Fulyzaq® / crofelemer
Dosage forms / Strength	Fulyzaq® (crofelemer) 125 mg tablet PO BID
Proposed Indication	Control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.
Recommended Action:	Approval (AP) under 21 CFR 314

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1 Introduction

This submission, received December 5, 2011, is the initial New Drug Application (NDA) for Fulyzaq® (crofelemer), a polymeric proanthocyanidin extracted from the red latex sap of the plant species Croton lechleri from the Amazon regions of South America.

The Applicant's proposed indication for crofelemer is:

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

Based on *in vitro* and *in vivo* studies, crofelemer is believed to be an inhibitor of both the cAMP stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel and the calcium-activated chloride channels (CaCC); the inhibition is believed to block chloride secretion and high volume water loss that occurs with diarrhea.

The proposed product is a delayed-release tablet. The proposed dose is 125 mg BID.

All the review disciplines recommend in favor of approval, but several Phase 4 commitments were recommended.

2 Background

2.1 Diarrhea in HIV/AIDS Patients

In the era of highly active antiretroviral therapies (HAART), diarrhea from opportunistic infections is uncommon.[1] No pathogen can be identified in 15-46% of HIV-infected patients with diarrhea.[2] HIV-associated diarrhea often has non-infectious causes including adverse effects of HAART (especially protease inhibitors), HIV enteropathy, HIV-associated malignancies, and pancreatitis.[3] Mechanisms of HAART-associated diarrhea include increased calcium-dependent chloride conductance and cellular apoptosis, necrosis and decreased proliferation of intestinal epithelial cells.[4]

Diarrhea is reported in up to 60% of patients with HIV infection.[5,6] However, precise prevalence estimates are difficult due to variations in defining HIV-associated diarrhea such as duration (acute versus chronic), definition of diarrhea, and assessment tools.[7]

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[1] MacArthur RD and Dupont HL. Etiology and pharmacologic management of noninfectious diarrhea in HIV-infected individuals in the highly active antiretroviral era. *Clin Inf Dis*; advance access published July 16, 2012.
[2] Kartalija M, and Merle AS. Diarrhea and AIDS in the era of highly active antiretroviral therapy. *Clin Inf Dis* 1999; 28:701-7.
[3] MacArthur and Dupont, 2012.
[4] Ibid.
[5] Ibid.
[6] Zingmond DS, Kilbourne AM, Justice AC, et al. Differences in symptom expression in older HIV-positive patients: the Veterans Aging Cohort 3 Site Study and HIV Cost and Service Utilization Study experience. J Acquir Immune Defic Syndr 2003; 33(Suppl 2): S84–92.
[7] MacArthur and Dupont, 2012.

HIV-associated diarrhea can have a substantial negative impact on quality of life.[8] The condition can result in lack of adherence to HAART regimens as well as the need to change HAART regimens.[9]

Currently, there is no product specifically approved for HIV-associated diarrhea. Anti-motility agents such as loperamide are often used. However, there are no clinical data to support the use of anti-motility agents for this condition.[10] Other treatments include non-narcotic, narcotic or anti-secretory medications. HAART regimen modification may also be attempted. Non-pharmacologic supportive treatment includes dietary modification such as fiber supplements.[11]

2.2 Crofelemer Regulatory History

The table below provides an overview of the regulatory activity of Crofelemer.

Table 1. Pertinent Regulatory History of Crofelemer*

Date	Event
November 1, 1996	IND submitted
May 5, 2004	End of Phase 2 Meeting
October 20, 2006	SPA Request received (Protocol for NP303-101)
December 1, 2006	SPA No Agreement Letter sent
January 16, 2007	Meeting to discuss SPA
March 14, 2007	Advice Letter with Statistical Comments
June 21, 2007	Advice Letter with Clinical/Statistical Comments
February 1, 2008	Advice Letter with Statistical Comments
July 30, 2007	New Protocol (Protocol for NP303-101) Submitted
August 4, 2008	Advice Letter with Clinical/Statistical Comments
January 19, 2011	Pre-NDA Meeting
May 24, 2011	Pre-NDA CMC Meeting
December 16, 2011	Submission of NDA

*IND 51,818

Key comments communicated to the sponsor during the meetings and review of the IND submission included the following:

(1) End of Phase 2 Meeting: At the End of Phase 2 Meeting, agreement was reached that the proposed Phase 3 study (NP303-101) would meet the requirements for an additional pivotal trial with supportive data from the 2 completed studies [Study 37554-209 (Phase 2; n=85) and Study 37554-210 (Phase 3; n=400)]. Also, agreement was reached that the primary endpoint will be the proportion of patients that are responders (where clinical response is defined as ≤ 2 watery bowel movements per week).

(2) Special Protocol Assessment: Agreement was not reached on the Special Protocol Assessment (SPA). However, the SPA No Agreement Letter (December 1, 2006) contained an agreement to modify the primary endpoint so clinical response is defined as

[8] Ibid.
[9] Ibid.
[10] Ibid.
[11] Ibid.

≤ 2 watery bowel movements per week during at least 2 weeks of the 4-week efficacy assessment period.

(3) Other Meetings/Advice Letters (post SPA No Agreement Letter): In subsequent discussions (after the SPA No Agreement Letter), there was agreement to use an adaptive design for the proposed Phase 3 study (NP303-101) and to use the Posch and Bauer method for combining the data from Stage I and II (see Statistical Review by Lisa Kammerman for more information regarding the adaptive design and the Posch and Bauer method).

It should be noted that there was a change of sponsor from Napo Pharmaceuticals, Inc. to Salix Pharmaceuticals, Inc. on December 9, 2009.

See the Clinical Review by Wen-Yi Gao for details of the Crofelemer regulatory history.

2.3 Current Submission

The NDA submission was received on December 5, 2011. It was classified as a six-month submission (Priority Review) with a PDUFA deadline of June 5, 2012; because of a major amendment received on April 6, 2012, the PDUFA date was extended to September 5, 2012. The review of this NDA submission was extended beyond the PDUFA date in order to allow time for the Applicant to develop and validate bioassays to evaluate the activity of crofelemer and for these methods to be reviewed; the Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP) was consulted to review the bioassay methods and validation results.

The relevant review disciplines have all written review documents; one of these is in **DRAFT** form as indicated below. The primary review documents relied upon were the following:

(1) Clinical Review by Wen-Yi Gao, dated October 3, 2012
(2) Statistics Review by Lisa Kammerman, dated December 18, 2012
(3) Office of New Drug Quality Assessment (ONDQA) CMC Reviews:
    (a) First Primary CMC Review by Nina Ni, dated July 13, 2012
    (b) Second Primary CMC Review by Nina Ni, **DRAFT** dated December 19, 2012
(4) Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP) Bioassay Review by Cristina Ausin-Moreno and Emanuela Lacana (entered in DARRTS by Howard Anderson), dated December 21, 2012
(5) Botanical Review Team (BRT) Reviews:
    (a) Primary Botanical Review by Jinhui Dou, dated August 8, 2012
    (b) Secondary Botanical Review by Shaw Chen, dated August 10, 2012
(6) Pharmacology/Toxicology Review by Sruthi King dated August 2, 2012
(7) ONDQA Biopharmaceutics Review by Mark Seggel dated August 1, 2012
(8) Clinical Pharmacology Review by Kristina Estes dated September 4, 2012
(9) Office of Scientific Investigations (OSI) Clinical Inspection Summary Review by Khairy Malek dated August 9, 2012

(10) Division of Medication Error Prevention and Analysis (DMEPA) Reviews:
   (a) DMEPA Label and Labeling Review by Manizheh Siahpoushan dated March 2, 2012
   (b) DMEPA Proprietary Name Review by Manizheh Siahpoushan dated March 9, 2012
   (c) DMEPA Proprietary Name Review by Anne Crandall Tobenkin and Lubna Merchant dated September 5, 2012
(11) Office of Prescription Drug Promotion (OPDP) Division of Professional Drug Promotion (DPDP) Review by Kathleen Klemm dated August 15, 2012
(12) Division of Antiviral Products (DAVP) Consult Review by Jeffrey Murray dated February 6, 2012
(13) Division of Risk Management (DRISK) Review by Carolyn Yancey dated August 31, 2012.
(14) QT Interdisciplinary Review Team (QT-IRT) Consult Reviews (filed under IND 51,818):
   (a) QT-IRT Consult Review by Monica Fiszman dated September 28, 2011
   (b) QT-IRT Consult Review by Monica Fiszman dated January 10, 2012
   (c) QT-IRT Consult Review by Janice Brodsky dated October 23, 2012

It should be noted that the following review is **PENDING** (at the time this CDTL Review was written):

► Tertiary CMC Review by Terrance Ocheltree (Director, Division of New Drug Quality Assessment II)

The Division of Antiviral Products (DAVP) was consulted regarding the appropriateness of the Applicant's request for a Priority Review. The DAVP consult review by Dr. Jeffrey Murray concluded that criteria for a Priority Review were met primarily because there are no approved therapies for HIV associated diarrhea, particularly for patients who have tried other anti-diarrheal medications not specifically approved for use in HIV.

The reviews should be consulted for more specific details of the application.

3 CMC

The reader is referred to the First Primary CMC Review, the Second Primary CMC Review, the OBP DTP Bioassay Review, the Primary Botanical Review, and the Secondary Botanical Review for complete information.

3.1 Overview

3.1.1 Overview of Botanical Raw Material (BRM)

The botanical raw material (BRM) (i.e., crude plant latex; CPL) is the red latex of *Croton lechleri* Müll.Arg. [Fam. Euphorbiaceae] commonly known as "Dragon's blood." The full taxonomic classification is provided in the Primary Botanical Review. The Primary Botanical Reviewer noted that the short list of synonyms to the species name of *Croton lechleri* Müll.Arg. (only two synonyms) suggests that the taxonomy of this species is

relatively straightforward. Also, the Primary Botanical Reviewer noted that there are two other closely related species that produce red latex and are present within the geographical range of *Croton lechleri* Müll.Arg. (*C. perspeciosus* Croizat and *C. erythrochilus*); however, *Croton lechleri* Müll.Arg. has distinctive characteristics that allow it to be easily identified. The CPL will be collected from specific geographic regions (Eco-Geographic Regions (EGRs) (b) (4) as CPL batches for clinical trials were supplied from these (b) (4) EGRs.

3.1.2 Overview of Drug Substance (DS)

The drug substance (DS) is manufactured by (b) (4) The DS is extracted and partially purified from the CPL of *Croton lechleri* Müll.Arg. The DS is an oligomeric/polymeric mixture of catechin, gallocatechin, and their epimers; it contains primarily proanthocyanidin oligomers with an average molecular weight of 1700 to 2500 Daltons. The DS manufacturing process involves the following (b) (4) The Primary CMC Reviewer noted that adequate in-process controls are in place for each intermediate step to reasonably maintain batch to batch consistency.

The First Primary CMC Review notes that establishment evaluation was requested for the (b) (4) and that the Office of Compliance issued an "acceptable" recommendation on 03/26/2012.

3.1.3 Overview of Drug Product (DP)

The drug product (DP) is manufactured by Patheon Pharmaceutical Inc. (Cincinnati, Ohio) in a process that entails (b) (4) , and final packaging (into 60-count high-density polyethylene bottles). The Primary CMC Reviewer noted that conventional tablet unit operations and equipment are used, and adequate in-process controls are in place.

A contract laboratory, (b) (4) uses an HPLC test to determine the oligomer composition and distribution.

The First Primary CMC Review notes that establishment evaluation was requested for the Patheon Pharmaceutical Inc., Cincinnati, Ohio site, and for the contract laboratory, (b) (4) , and that the Office of Compliance issued an "acceptable" recommendation for the two sites on 03/26/2012.

3.2 Issues

In the First Primary CMC Review, the Primary CMC Reviewer identified issues regarding the identity, strength, purity, and quality of the drug substance and drug product. Citing 21

CFR 314.125(b)(1), the Primary CMC Reviewer initially concluded that these issues preclude approval.

The Botanical Reviewers concluded that the submitted CMC information supported approval.

Both the ONDQA and BRT perspectives were presented at a Center Director Briefing on August 6, 2012 (see Section 9 of this CDTL Review) and are summarized below (from the Center Director Briefing Document, the First Primary CMC Review, the Primary Botanical Review, and the Secondary Botanical Review).

The resolution of these issues are also summarized below (from the Second Primary CMC Review and the OBP DTP Bioassay Review).

3.2.1 ONDQA Perspective

Primary Concern

The primary ONDQA concern is the lack of a reproducible and robust test for the identity of the drug substance. Such a test is necessary in order to:
(a) determine if the proposed commercial product is comparable to the product used in clinical trials;
(b) assure comparability among commercial lots of drug product; and
(c) detect intentional or unintentional adulteration of the drug substance.

Applicant's Initial Proposal

The Applicant's initial proposal was to identify drug substance using IR (b) (4) tests and an HPLC test. See the First Primary CMC Review.

IR and (b) (4) Tests: The ONDQA reviewers concluded that the IR and (b) (4) tests are not specific.

HPLC test: The HPLC method involves the laboratory depolymerization via hydrolysis of the oligomeric/polymeric material into its constituent monomers, allowing calculation of the monomer ratio of (epi)catechin to (epi)gallocatechin, average molecular weight, and conversion yield (depolymerization). The ONDQA Reviewers noted the following:
(1) (b) (4)
(2) Recent communications with the applicant have revealed that this depolymerization process may not be reproducible or robust.
The ONDQA Reviewers concluded that the HPLC method is not suitable for identification without further development.

Other Concerns

Other concerns due to the absence of adequate tests for identity were noted. It is necessary to assess the oligomer/polymer distribution in order to:
(a) detect the source of the proanthocyanidin, and
(b) assure the consistency and clinical effectiveness of the drug substance and drug product.

The impact on the utility of other tests (such as stability tests) was also noted.

First Primary CMC Review

ONDQA concluded that without appropriate tests for identity, the safety and efficacy of the product cannot be assured. ONDQA also commented that the Applicant's proposed tests for identity fail to meet the minimal recommendations cited in the Botanical Guidance (2004 Guidance for Industry: Botanical Drug Products). Specifically, ONDQA noted that the Botanical Guidance recommends for Phase 3:
Botanical drug substance (21 CFR 312.23(a)(7)(iv)(*a*)):
- A chemical identification for the active constituents or characteristic markers in the drug substance, if possible. If the chemical identity is unknown, a representative spectroscopic and/or chromatographic fingerprint may suffice.
- Biological assay (when the active chemical constituents are not known or quantifiable)

Botanical drug product (21 CFR 312.23(a)(7)(iv)(*b*)):
- Chemical identification for the active constituents or, if unknown, the characteristic markers
- Stability-indicating analytical methods

A full listing of deficiency items identified by the Primary CMC Reviewer is summarized below (taken from Pages 196-197 of the First Primary CMC Review):

1) Regarding Specifications for the Drug Substance and Drug Product
   a) Identity
      - The specification of the drug substance does not have a reliable test for demonstrating consistent distribution of oligomers (b) (4) above) with an acceptance criterion for each oligomer.
      - The IR spectroscopic test in the drug substance specification has not been demonstrated that the spectra obtained from testing samples are comparable to that obtained from the reference standard. Need to compare all available IR spectra generated from all clinical and stability batches of crofelemer drug substance with that of the reference standard.
      - Satisfactory review of analytical procedure and its validation report for PC/PD ratio, mean degree of polymerization, conversion yield, and oligomer composition and distribution determination is needed.
      - Even [if] all these issues are satisfactorily resolved, all identity tests as a whole will still be far from fulfilling the statutory requirement for establishing the identity of a drug. This is a fundamental deficiency.
   b) Purity

- [redacted]
- Satisfactory review of analytical procedure and its validation report for [redacted] is needed.
- The proposed acceptance criterion of NMT [redacted] for heavy metals should be tightened to [redacted]
- The applicant needs to commit to develop, within one year of the approval date of this NDA, a stability indicating analytical methods for Related Substances in the drug substance and drug product.

c) Strength
- The applicant needs to commit to develop, within one year from the approval date of this NDA, stability indicating analytical methods for the Assay in the drug substance and drug product.

d) Quality
- The proposed dissolution test and acceptance criterion should be revised as follows:
  - Acid Stage: no individual unit exceeds [redacted] dissolved at 2 hours, rather than [redacted] as proposed.
  - Buffer Stage: Q = [redacted] at 45 minutes, rather than Q = [redacted] minutes.

e) Other
- The drug product specification should be updated with the acceptance criterion for 'Appearance' to reflect the imprint on the tablets.

2) Regarding Stability
- Revise the proposed storage condition for the drug substance to [redacted] with excursion permitting to [redacted].
- The post-approval stability protocols for both drug substance and drug product need to be updated to remove [redacted] test in both drug substance and drug product specifications and add [redacted] and oligomer composition and distribution tests in drug substance specification.
- Insufficient stability data is provided to justify the proposed shelf life of 24 months for drug product.

3) Regarding DMF [redacted]
- An information request was sent to the holder of DMF [redacted] The applicant is asked to contact DMF holder to address all pending issues.

4) Regarding Labels and Labeling

a) "Full Prescribing Information" Section
  (i) Strength needs to be provided.
  (ii) Word of [redacted] needs to be changed to imprinted

b) "Description" Section
  (i) Describe pharmacological/ therapeutic class
  (ii) Delete the structural formula
  (iii) Delete the statement of "[redacted]

c) "How Supplied" Section

(i) Add the strength of dosage form.
(ii) Add the identification of dosage form.
(iii) Add storage condition.

d) "Carton Label"
(i) Need to provide carton label.
(ii) Need to revise the dosage form to delayed-release tablets

These label/labeling comments will be conveyed to the applicant during the labeling discussion with the applicant.

Second Primary CMC Review

The deficiency items identified in the First Primary CMC Review (listed above) were re-evaluated in the Second Primary CMC Review based on amendments submitted by the Applicant.

The CMC Reviewer noted that all of the items in had been resolved with the exception of three items that can be addressed as postmarketing commitments (see Section 13.6 of this CDTL Review).

The resolution of each of the items (listed above) is summarized below from the Second Primary CMC Review:

Item 1a, Identity: The CMC Reviewer concluded that the Applicant's response to each of the parts of this item was acceptable.

- Test for Demonstrating Consistent Distribution of Oligomers: The Applicant updated the drug substance specification (b) (4) the CMC Reviewer noted that given the heterogeneity of this type of product, the proposed limits are considered acceptable.
- Comparability of IR Spectra to Reference Standard: The Applicant provided IR spectra from all lots of drug substance used for Phase 3 clinical trials and stability drug product batches. The CMC Reviewer noted that a reasonably concordant IR spectrum (exhibits comparable characteristic fingerprints) can be obtained from different lots of crofelemer when compared to that of reference standard of crofelemer. The CMC Reviewer commented also that the IR spectra obtained from crofelemer appear to be reasonably specific and show much more detailed and different fingerprints than those of other proanthocyanidins, making the IR measurement sufficient enough to serve as a part of the identification tests.
- Validation Data (PC/PD ratio, Mean Degree of Polymerization, Conversion Yield, and Oligomer Composition and Distribution Determination): The Applicant revised the analytical method; the validation data were deemed adequate by the CMC Reviewer.
- Concern that Above Identity Tests Insufficient for Establishing Identity: The CMC Reviewer noted that the identity/structure for crofelemer is not fully established/defined. (b) (4)

(b) (4) . Thus, to confirm their claim, the drug substance manufacturer is actively pursuing a new elemental analysis using current up-to-date technology, and will submit this information upon completion of the analysis as part of a postmarketing commitment (see **CMC PMC #1** in Section 13.6 of this CDTL Review). The CMC Reviewer noted that despite the uncertainties regarding the structure of crofelemer ((b) (4) the updated tests and specifications for 1) oligomer distribution, 2) IR measurement, 3) monomer ratios, 4) mean degree of polymerization, and 5) conversion yield after hydrolysis, as described and discussed in their validation reports, is considered to be sufficient for establishing the identity of crofelemer, because a fully validated and clinically relevant bioassay has also been implemented as part of the drug substance and drug product specifications. The CMC Reviewer commented that the Applicant has committed to characterizing the (b) (4) as a postmarketing commitment (see **CMC PMC #2** in Section 13.6 of this CDTL Review). .

Item 1b, Purity and Item 1c, Strength: The CMC Reviewer concluded that the Applicant's response to each of the parts of these items was acceptable.

- (b) (4): The CMC Reviewer noted that the (b) (4) in the equation to calculate (b) (4) content has been corrected.
- Analytical Procedure and Validation Report for (b) (4) The analytical procedure and validation report for (b) (4) was deemed adequate by the CMC Reviewer.
- Proposed Acceptance Criterion for Heavy Metals: The proposed acceptance criterion for heavy metals was tightened from NMT (b) (4) to (b) (4) as requested.
- Stability Indicating Analytical Methods (Assay and Related Substances): The Applicant committed to develop, within one year of the approval date of this NDA, stability indicating analytical methods for assay and related substances in the drug substance and drug product (see **CMC PMC #3** in Section 13.6 of this CDTL Review).

Item 1d, Quality: The proposed dissolution test and acceptance criteria were revised as requested (see Biopharmaceutics Review in Section 5.1.2 of this CDTL Review).

Item 1e, Other: The drug product specification was updated with the acceptance criterion for "Appearance" to reflect the imprint on the tablets as requested.

Item 2, Stability: The CMC Reviewer concluded that the Applicant's response to each of the parts of this item was acceptable.

- Proposed Storage Condition for the Drug Substance: The Applicant revised the proposed storage condition for the drug substance to (b) (4) with excursion permitting to (b) (4).
- Update of Post-Approval Stability Protocols: As requested, the Applicant updated the post-approval stability protocols for both drug substance and drug product to remove (b) (4) tests from both drug substance and drug product specifications, and oligomer composition and distribution tests based on (b) (4) and HPLC analysis were added to the drug substance specification.
- Insufficient Stability Data: As requested, the Applicant provided 24-month stability data to support the proposed expiration dating period of 24 months for the drug product.

Item 3, DMF (b) (4): The CMC Reviewer noted that issues with the DMF holder have been successfully resolved.

Item 4, Label and Labeling: The CMC Reviewer noted that label and labeling issues have been resolved.

Conclusion

In the Second Primary CMC Review, the CMC Reviewer noted the following as the basis for approvability:

- The botanical raw materials are well controlled.
- Manufacturing process and in-process controls are deemed adequate.
- Specifications for the botanical drug substance and botanical drug product are considered adequately validated to assure the identity, strength, purity and quality of the drug product.
- Clinically relevant bioassays for the drug substance and drug product are also considered to be acceptable for assuring therapeutic consistency of the drug product (citing the Bioassay Review).
- Stability of the drug product is reasonably demonstrated to be adequate for assuring a 24-month expiration dating period.

3.2.2 BRT Perspective

The Secondary Botanical Reviewer noted that botanical new drugs can rarely have CMC specifications as precise as those of pure chemical drugs. He commented that it is especially difficult to determine for botanical drugs with unknown number and identities of active ingredients (such as crofelemer) whether the future marketing batches will have the same therapeutic effects as that observed in clinical trials.

He proposed that one or more elements of the schema below (though not part of the current Botanical Guidance) can address the concern that future marketing batches may not have the same therapeutic effects as that observed in clinical trials.

(1) Pre-CMC Control

The Botanical Secondary Reviewer noted that crofelemer is a relatively simple botanical (single part of a single plant) with a class of well-studied active compounds (oligomers of catechins). Also, he noted that identification of the plant is straightforward and there is little risk of confusion with other species. Further, the collection of crude plant latex from wild-grown trees will be restricted in (b) (4) eco-geographic regions with GACP (good agricultural and collection practices) implementation to minimize variation at the plant level. He further pointed out that, in general, latex is less variable than other parts of the plant, such as leaf. Finally, he suggested that Current Good Manufacturing Practices (cGMP) should start at the botanical raw material level.

(2) Standard CMC Measures

The Botanical Secondary Reviewer noted that the multiple analytical chemical techniques to monitor the chemical composition of the drug substance are adequate from both the regulatory and technical feasibility standpoints; he commented that the analyses should be conducted as extensively as the technology and practical considerations allow. Further, he suggested that, as for the botanical raw material, controls in processes should be emphasized.

(3) Post-CMC Evidence

Phase 3 Clinical Trial Data: The Botanical Secondary Reviewer noted that multiple batches of crofelemer have been used in Phase 3 clinical trials, and that although the sample numbers are too small for formal statistical analysis, there is no sign suggesting certain batches were more effective than others.

Mechanism of Action Studies: The Primary Botanical Reviewer[12] (citing the Applicant's Summary of Clinical Pharmacology[13]) noted that the estimated gastrointestinal lumen concentration following oral administration of the 125 mg BID dose is 178 μM. He noted that the IC50 is 7 μM for CFTR-mediated Cl^- secretion in T84 cells (source is Tradtrantip et al., 2010[14]) and that the IC50 is 50 μM for Caco-2 cells (source is Primary Pharmacology Study SP-303-E-068). Thus, the estimated gastrointestinal lumen concentration was 25-fold and 3.6-fold greater than the IC50 for CFTR-mediated Cl- secretion in T84 cells and Caco-2 cells, respectively. The Botanical Secondary Reviewer noted that these mechanism of action studies suggest that the inhibition of chloride channels is fully saturated at the dose range of 125-500 mg suggesting that the clinical response rates are most likely not affected by minor variations in the quantitative composition of procyanidin oligomers and making other uncontrollable variations and uncertainties less critical to clinical response.

Wide-Spread Use: Finally, the Botanical Secondary Reviewer noted that wide-spread use of crofelemer to treat diarrhea in Central and South America suggests that the self-assessable

[12]Page 41 of the Primary Botanical Review by Jinhui Dou dated August 8, 2012
[13] Module 2.7.2.5.1 In Vitro Studies of Crofelemer Mechanism of Action
[14] Tradtrantip L, Namkung W, Verkman AS. Crofelemer, an antisecretory antidiarrheal proanthocyanidin oligomer extracted from Croton lechleri, targets two distinct intestinal chloride channels. Mol Pharmacol 2010 Jan;77(1):69-78.

benefit is fairly consistent in a large population for a long period of time. He concluded that very detailed control of the botanical drug apparently was not necessary for such consistency in indigenous use.

Conclusion

The BRT concluded that there is adequate assurance of the therapeutic consistency of future marketing batches based on the above schema of pre-CMC control and post-CMC evidence in addition to standard CMC measures.

3.2.3 Bioassay Development

Review Team's Request

The Review Team concluded that a request to develop a bioassay that would allow for potency testing and for release and stability testing on future batches of crofelemer should be communicated to the Applicant. This is consistent with the recommendation from the Center Director Briefing (See Section 9 of this CDTL Review).

In response to the request to develop a bioassay (in teleconferences with the Applicant on August 6, 2012, and August 8, 2012), the Applicant submitted an information amendment dated August 10, 2012, which included the current status and proposed timeline for bioassay development (for purposes of ensuring lot-to-lot consistency and stability).

The review team consulted the Office of Biotechnology Products (OBP) Division of Therapeutic Proteins (DTP) to review the bioassay proposed by the Applicant (see OBP DTP Review by Cristina Ausin-Moreno and Emanuela Lacana).

Applicant's Proposal

The Applicant's proposal (August 10, 2012) and the OBP DTP Bioassay Reviewers' assessment of that proposal are summarized below.

Proposed Model: (b) (4)

(b) (4)

(b) (4) [redacted]

Method Development: The methods will be developed, validated, and utilized according to the principles described in: (a) the Botanical Guidance; (b) USP 35 <1032>; and (c) USP 35 <1033>. The Applicant noted the following three salient recommendations of these documents: (1) Use of an assay with a clinically relevant endpoint; (2) In the case of *in vitro* cell models, the use of stable transfected cell lines to improve response, constancy of receptor expression, cell availability, and overall assay stability; and (3) Comparison of relative potency of the test article to a positive control with known activity in the assay, to compensate for the inherent variability in biological test systems.

(b) (4) [redacted].

For the initial examination, three lots of drug substance and three corresponding lots of tablets will be used. The studies will be conducted by the (b) (4) [redacted].

Timeline: The timeline proposed by the Applicant is as follows:

- (b) (4) [redacted]

The Bioassay Reviewers concluded that the proposed timeline is not feasible. The Bioassay Reviewers commented that in the experience of OBP/DTP, it is likely that assay development and validation will require a time-frame significantly longer than the one proposed by the Applicant.

The Bioassay Reviewers had the following specific concerns:

- GMP Compliance Status: The proposed release and stability testing site does not appear to be operating under Good Manufacturing Practice (GMP). Quality Control laboratories for release and stability testing are required to be in compliance with GMPs.
- Site Inspection: The site (b) (4) [redacted] runs assays according to Good Laboratory Practice (GLP) specifications, and was last inspected by the FDA (GLP audit) in 2004. Therefore, an inspection would have to be scheduled and conducted. The inspection time frame usually depends on the availability of field inspectors and often this requires several months; however, for unmet medical need, perhaps the inspection could be speedily arranged.
- Timeline: The proposed plan does not contain sufficient information to establish the feasibility of developing the assay within the proposed timeline. For example, there is no

[17] Ibid.
[18] Ibid.

description of the development and optimization procedures for the bioassay. The Applicant provided (b) (4) [redacted]. Additionally, the Applicant proposes to use (b) (4) [redacted].

Bioassay Validation

Analytical Procedures and Validation Protocol

(b) (4) [redacted]

(b) (4)

Additional Communication: Additional communication with the Applicant is summarized below.

The following comments were sent to the Applicant:

- Please propose appropriate drug substance (API) and drug product (125 mg tablets) release and stability acceptance criteria for the Crofelemer potency bioassay (Advice Letter dated December 10, 2012).
- Acceptance criteria should include IC_{50} and maximum block relative to CFTRinh-172 (communicated to the Applicant on December 11, 2012 as per the Bioassay Review).

The Applicant proposed the following:

- Acceptance criterion of (b) (4) relative potency (teleconference on December 14, 2012[19]).

Final Validation Report

The Final Validation Report (CFTR assay) was received on December 14, 2012. A summary of the Bioassay Reviewer's assessment is presented below.

System Suitability Acceptance Criteria: The Applicant proposed the following system suitability acceptance criteria: (b) (4) The Applicant proposed to finalize post-validation any necessary additional system suitability criteria. The Bioassay Reviewers concluded that this was acceptable.

Linearity and Repeatability (Precision): The Applicant determined the linearity of the results for reference standard (RS), DS, DP, and CFTRinh-172 (positive control) over a range of concentrations (1 to 560 µM) in two different curves (the first ranging from 1to 300 µM and the second ranging from 3 to 560 µM).

- IC50: The Bioassay Reviewers commented that the calculated IC50 concentration for all three materials (RS, DS and DP) is within the range of concentrations tested during the validation, and the correlation coefficient is (b) (4)
- %RSD: The Bioassay Reviewers graphed the percent relative standard deviation (%RSD) versus concentrations, and noted that the %RSD is higher at lower concentrations; the Bioassay Reviewers noted that this is not an unexpected result because the variability in the current measurements is higher at lower sample concentrations. The Bioassay Reviewers concluded that if the two lowest concentrations are ignored, the %RSD range is as follows: (b) (4) The Bioassay Reviewers noted that the highest variability in the

[19] Email from Emanuela Lacana dated December 14, 2012.
[20] Criterion for % Inhibition of crofemeler reference standard of (b) (4) was added on 12/20/2012.

results corresponds to DS, and that such %RSD values are common for cell-dependent bioassays.

- Hill coefficient: The Bioassay Reviewers noted that the calculated Hill coefficient values range between (b) (4), with very similar results for DS (b) (4) and DP (b) (4); they noted that the maximum blocks (relative to CFTRinh-172) obtained for DS and DP are equivalent (b) (4) respectively), and that the RS causes a smaller block (b) (4)).

The Bioassay Reviewers could not make any conclusions regarding any potential differences in the quality of the lots causing the difference in chloride channel block because the submission included a Certificate of Analysis for the RS but limited release data for the remaining 6 lots (material from 3 DS and 3 DP batches that were used to develop and validate the bioassay as per the Applicant). However, the Bioassay Reviewers noted that the preliminary results submitted on 10/10/2012 showed a mean block of (b) (4) for DS and DP respectively, and that published data (Mol. Pharmacol, 77:69-78, 2010) report a maximum block of ~60% and IC50 of ~ 7µM for crofelemer tablets. The Bioassay Reviewers recommended that either the acceptance criterion or the system suitability requirements include an acceptable range for the maximum block caused by crofelemer. The final proposal from the Applicant was an acceptance criterion of (b) (4) current inhibition for the reference standard; the Bioassay Reviewers agreed with this criterion.

Method Precision:

- IC50: The Applicant calculated IC50 for six independent DS preparations and six independent DP preparations in order to determine the precision of the method, and tested each of the independent preparations in duplicate. The Bioassay Reviewers concluded that there are no significant differences in the percentage of maximum block and the IC50 obtained during the determination of the intermediate precision for DS or DP.
- %RSD: The Bioassay Reviewers noted that the %RSD is higher for DP, but the higher % RSD is probably caused by one single point, and it is likely that excluding the data point would result in a lower % RSD. The Bioassay Reviewers concluded that the results are acceptable.
- Accuracy: The Bioassay Reviewers noted that the assay does not perform as well at higher nominal potency of crofelemer, and although not optimal, this level of accuracy is acceptable, because the accuracy is within (b) (4) of the nominal values at lower concentrations, suggesting that the assay is suited to estimate loss of potency.
- Robustness: The Applicant evaluated robustness by analyzing the effect of sample solution stability, extraction efficiency of crofelemer tablets, and cell culture conditions. The Bioassay Reviewers concluded that these studies showed that there is minimal effect of cell passage or vortex time on assay performance; the assay performance was affected by the age of the sample solutions. The Bioassay Reviewers commented that (b) (4) appropriately recommended that sample solutions be prepared the day of use.
- Specificity: The specificity assessment included the evaluation of matrix, related substances and degraded samples. The Bioassay Reviewers noted that neither matrix (b) (4), nor related substances (b) (4) inhibit the assay, and that forced degradation studies conducted using a variety of stress conditions indicated that the assay could be stability-indicating. The Bioassay Reviewers concluded that the assay is suitable to detect changes in the product; they noted that base and acid treatment reduce

potency to (b) (4) of the untreated samples, heat and oxidation cause moderate reduction in the relative potency of the assay, and light does not cause significant shifts in the potency curve.

Acceptance Criteria: The Applicant proposed an acceptance criterion for the bioassay of (b) (4) based on pooled results obtained from the bioassay validation on drug substance and drug product. The Bioassay Reviewers noted that the Applicant's proposal is acceptable because the Applicant was asked to establish this assay very late in drug development. The Bioassay Reviewers commented that this approach is not optimal, as typically acceptance criteria are established based on the results of the material used in the clinical trial. In this case, the typical approach is not feasible because the Applicant has little to no clinical trial material still available. The Bioassay Reviewers noted that the Applicant also proposes to evaluate any historical material available and accumulate all release and stability data on post-approval lots, and to re-evaluate the specification and the need for a revision of the specification.

Inspectional Item: The Bioassay Reviewers noted that the field investigator inspecting the (b) (4) facility identified an issue with the (b) (4). The Bioassay Reviewers noted that (b) (4) . In the assay system suitability, (b) (4) set a lower acceptance limit for the (b) (4) (b) (4) In order to better control the performance of the assay, the Bioassay Reviewers previously requested that a minimum % inhibition range (b) (4) be included as an acceptance criterion in the system suitability; this system suitability acceptance criterion will also allow control for (b) (4). The Applicant agreed with this proposal in a teleconference on December 20, 2012.

GMP Inspection

GMP inspection of the (b) (4) facility started on (b) (4), and the results of the inspection are pending at the time of this CDTL Review.

Conclusion

The Bioassay Reviewers concluded that the validation report provided by the Applicant indicates that the assay is of sufficient accuracy and precision and the data support the suitability of the assay for release and stability of crofelemer. The Bioassay Reviewers noted that the proposed specification of (b) (4) relative potency is also acceptable. The Bioassay Reviewers suggest conducting improvements to the assay and acceptance criteria through postmarketing commitments (PMC's) (see Section 13.6 of this CDTL Review).

The GMP inspection of the (b) (4) facility is pending at the time of this CDTL Review.

3.3 Recommendation

CMC: Although the First Primary CMC Review noted that there were deficiencies identified in the NDA that precluded approval of this application, the Second Primary CMC Review noted that those deficiencies had been resolved, and recommends approval. Three PMC's are recommended (see Section 13.6 of this CDTL Review).

BRT: Both the Primary and Secondary Botanical Reviews recommend approval.

Bioassay: The Bioassay Reviewers recommend approval of the cell-based assay for crofelemer, pending a favorable inspection of the testing facility and a favorable recommendation from the Office of Compliance. Two PMC's are recommended (see Section 13.6 of this CDTL Review).

4 Nonclinical Pharmacology/Toxicology

4.1 Issues

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Sruthi King dated August 2, 2012, for complete information.

The Applicant conducted pharmacology, pharmacokinetics, general toxicology, genetic and reproductive toxicology studies.

The Nonclinical Reviewer noted the following key findings:

- Crofelemer was shown to inhibit chloride ion secretion via cAMP/cGMP-mediated mechanism and decrease in fluid accumulation in an *in vivo* mouse model of secretory diarrhea.
- In safety pharmacology studies, crofelemer did not show any effects on cardiovascular, respiratory, neurobehavioral, or GI motility in rats at the highest dose tested (600 mg/kg).
- Crofelemer was shown to be poorly absorbed after oral administration in rats, with ~1% bioavailability, while ~99% remained in the GI tract, suggesting that it acts locally in the GI tract.
- *In vitro*, crofelemer produced dose-dependent inhibition of hERG (human ether-a-go-go) K^+ current; however, because of its low oral bioavailability, the potential risk of QT prolongation due to <2% free crofelemer is likely minimal to none. Plasma concentrations of crofelemer were low even at the highest doses evaluated (up to 1200 mg/kg/day for 56 days in mice). Crofelemer was highly bound to human plasma proteins and precipitated pepsin but did not induce CYP metabolic enzymes.
- In dogs, chronic oral administration of crofelemer for 9 months was not fatal but did produce dose-dependent gastrointestinal (GI) toxicity (emesis, abnormal excreta, diarrhea) and histological changes related to GI tract irritation and macrophage infiltration in the lymph nodes at doses greater than 175 mg/kg/day. At the highest dose tested (600 mg/kg/day), crofelemer produced significant decreases in body weight and food consumption and changes in clinical chemistry indicative of nutritional deficits.

The NOAEL dose in dogs was 50 mg/kg/day, based on GI-related clinical signs at doses of ≥175 mg/kg/day.

- When administered chronically in mice and rats, crofelemer produced deaths at doses above 40 mg/kg/day, in some cases due to dosing-related injuries; however, the cause of death of many of these animals was not known.
- In rhesus monkeys, dose-dependent histopathological changes (increased presence of pigmented macrophages) in the small intestine and cecum were observed when crofelemer was administered orally at up to 100 mg/kg/day for 30 days.
- In an embryofetal development study in rabbits, there was an increase in the number of resorptions and abortions in animals treated with 400 mg/kg/day (8 abortions/resorptions) crofelemer, as compared to control treatment (3 abortions). Maternal toxicity, as indicated by decreases in body weight and food consumption, was observed in control and high dose animals. It is unclear whether the effects of crofelemer on the litters (resorptions and abortions) are secondary to maternal toxicity.
- Crofelemer was not teratogenic in rats and showed no evidence of impairment of fertility in male or female rats at oral doses of up to 738 mg/kg/day. In a rat pre- and postnatal development study, crofelemer at oral doses of up to 738 mg/kg/day did not affect F_0 pregnancy and lactation, and survival, sex ratio, physical and neurobehavioral development, or reproductive performance of F_1 animals. Maternal (F_0) exposure to crofelemer did not affect fertility parameters of F_1 animals or embryonic development of F_2 generation.
- Crofelemer was also tested in juvenile animals. When administered daily by oral gavage to rats for 14 days (postnatal days 5 to 18) at doses of 50 and 100 mg/kg/day, there were 4 deaths (2 at high dose and 2 at low dose; none in control). There were also decreases in body weight at both doses tested and clinical chemistry changes, as compared to control. In juvenile monkeys (age 6-8 weeks), crofelemer was administered by oral gavage at 10, 200 and 500 mg/kg/day for 2 weeks. Lymphoid depletion from the thymus was observed at 200 and 500 mg/kg/day and the no effect dose was 10 mg/kg/day.

The Nonclinical Reviewer noted that the NOAEL dose in dogs provides a sufficient margin of safety for the recommended total daily dose of 250 mg/day (125 mg BID) and concluded that from a nonclinical standpoint, there are no significant safety concerns for the proposed dose for the proposed indication (i.e., control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy).

The Nonclinical Reviewer recommends an Approval action based on the non-clinical review of the information submitted in the NDA. The Nonclinical Reviewer additionally recommends that the proposed labeling be revised to include the following:

Section 8.1 of Label (Pregnancy):

Wording in the Pregnancy section should be revised to:

> "**Pregnancy Category C**.
> Reproduction studies performed with crofelemer in rats at oral doses up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of impaired fertility or harm to the fetus. In pregnant rabbits, crofelemer at an oral dose of about 96

times the recommended daily human dose of 4.2 mg/kg, caused abortions and resorptions of fetuses. However, it is not clear whether these effects are related to the maternal toxicity observed. A pre- and postnatal development study performed with crofelemer in rats at oral doses of up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of adverse pre- and postnatal effects in offspring. There are, however, no adequate, well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

Section 10.0 of Label (Overdosage):

Wording in the Overdosage section should be revised to:

"There has been no reported experience with overdosage of crofelemer (b) (4)

Section 13.1 of Label (Carcinogenesis, Mutagenesis, Impairment of Fertility):

Wording in the Carcinogenesis, Mutagenesis and Impairment of Fertility section should be revised to:

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

Mutagenesis
Crofelemer was negative in the bacterial reverse mutation assay, chromosomal aberration assay, and rat bone marrow micronucleus assay.

Impairment of Fertility
Crofelemer, at oral doses of up to 738 mg/kg/day (177 times the recommended human daily dose of 4.2 mg/kg) had no effects on fertility or reproductive performance of male and female rats."

Section 13.2 of Label (Animal Toxicology and/or Pharmacology):

The pharmacology/toxicology reviewer concluded that this section is not relevant and should be deleted.

4.2 Recommendation

An Approval Action is the recommendation by the Nonclinical Pharmacology/Toxicology discipline provided the labeling revisions described above are made. In addition, there is a

recommendation for two postmarketing requirements (PMR's) (see Section 13.5 of this CDTL Review.)

5 Clinical Pharmacology/Biopharmaceutics

5.1 Issues

5.1.1 Clinical Pharmacology

The reader is referred to the Clinical Pharmacology Review by Kristina Estes for complete information.

The Clinical Pharmacology Reviewer notes that the Applicant has submitted the results of nine Phase 1 studies, a Phase 2 study, and two Phase 3 trials. The Phase 1 studies in healthy volunteers included four single- and multiple-dose pharmacokinetic (PK) studies, three studies of the maximum tolerated dose, one drug-drug interaction study, and one food effect study. (See Appendix 1 of this CDTL Review.)

The Clinical Pharmacology Reviewer also notes that the Applicant has submitted some data from several *in vitro* studies of crofelemer that addressed the following: plasma protein binding, Caco-2 permeability, CYP inhibitory potential, and transporter inhibitory potential.

Clinical pharmacology findings are summarized below.

PK in Healthy Volunteers and Patients:

The systemic exposure of crofelemer was very low in healthy volunteers and patients; therefore, the PK was not able to be fully characterized. Results from the food effect study, which included rich sampling and the most sensitive assay (LC/MS/MS with an LOQ of 50 ng/mL), showed only two samples with detectable crofelemer (54.7 and 70.7 ng/mL). Trough blood samples collected in the NP303-101 trial and also analyzed using the most sensitive assay method detected crofelemer in only 15 of 456 samples with a maximum concentration of 77 ng/mL. The Clinical Pharmacology Reviewer noted that crofelemer, a proanthocyanidin, is described by the Applicant as a polymer and is made up of linear chains of catechin, epicatechin, gallocatechin, or epigallocatechin monomer units; these chains reportedly range from 1 to 28 units, with an average length of 5 to 7 units. The Clinical Pharmacology Reviewer commented that data from the literature (citing an article by Manach et al.[21]) confirms that proanthocyanidin polymerization greatly impairs intestinal absorption.

Metabolism:

The metabolism of crofelemer, *in vitro* or *in vivo*, was not determined by the Applicant. The Clinical Pharmacology Reviewer commented that data from the literature (citing an article by

[21] Manach et al., "Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies", *Am J Clin Nutr* 2005;81(suppl):230S– 42S.

Manach et al.[22]) suggest that gut microflora are responsible for degradation of proanthocyanidins; the Clinical Pharmacology Reviewer noted that data from crofelemer are not available in humans.

Drug Drug Interactions:

Potential inhibition of Cytochrome P450 (CYP) enzymes and the potential to interact with antiretroviral (ARV) treatments was summarized by the Clinical Pharmacology Reviewer as follows:

- CYP Enzymes: The results of *in vitro* studies suggest that crofelemer has the potential to inhibit Cytochrome P450 (CYP) 3A4 at the concentration expected in the gut. Inhibition of other CYPs is also possible, however, only 3A4 is widely expressed in the gut; thus, the Clinical Pharmacology Reviewer recommended an *in vivo* study to evaluate the potential for crofelemer to interact with 3A4 substrates (see CP PMC #1 below). The Clinical Pharmacology Reviewer also noted that the Applicant has characterized the inhibitory potential of (b) (4) crofelemer on P450 enzymes, but did not perform this study with the drug substance (b) (4) Thus, the Clinical Pharmacology Reviewer recommends that *in vitro* studies be conducted to determine whether crofelemer is a substrate, inhibitor, or inducer of cytochrome P450 (CYP) enzymes and transporters expressed in the gut (see CP PMC #2 below). The Clinical Pharmacology Reviewer commented that inhibition of CYP enzymes in the liver is unlikely given systemic exposure to crofelemer is very low.
- ARVs: The potential for crofelemer to interact with ARVs was explored in Study 37554-103. Crofelemer (500 mg Q6H) was administered to 28 healthy volunteers for five days. Three ARVs (nelfinavir, zidovudine, and lamivudine) were administered as a single dose together on Day 5. The results of the study showed that crofelemer had no effect on the exposure of zidovudine and nelfinavir; however, there was a 20% decrease in lamivudine exposure. However, the interaction with lamivudine was not deemed to be clinically important even under conditions of use in standard clinical practice.

Dose-Selection:

The dose-response for crofelemer in Study 37554-210 and Stage 1 of Study NP303-101 is summarized below:

- Study 37554-210: Study 37554-210 used a stool weight endpoint (see Appendix 3 of this CDTL Review). The doses selected for 37554-210 were 250 mg and 500 mg QID and placebo. In Study 37554-210, there was no clear dose-response and no consistent response relative to placebo.
- Stage 1 of Study NP303-101: Stage 1 of Study NP303-101 used an endpoint of clinical response (see Section 7.1 of this CDTL Review). The doses selected for Study NP303-101 (Stage 1) were 125 mg, 250 mg, and 500 mg BID for 4 weeks versus placebo (in the PC phase). Then, patients treated with crofelemer in the PC phase continued the same dose in the PF phase.; patients that received placebo in the PC phase were re-randomized 1:1:1 to one of the three crofelemer dose regimens (125, 250, or 500 mg BID) in the PF phase. In Study NP303-101, there was no apparent dose response among the three dose

[22] Ibid.

groups, but numerically higher clinical response rates were observed in all three dose groups compared to placebo.

The Clinical Pharmacology Reviewer noted that multiple dose levels were not included in the Phase 2 study (Study 37554-209), which assessed stool weight following a 4-day treatment with 500 mg crofelemer QID (see Appendix 3 of this CDTL Review). The Clinical Pharmacology Reviewer also noted that only Study NP303-101 supports the application at the proposed dose, and that the other studies used different endpoints, dosing regimens, treatment duration, and crofelemer formulations.

Pharmacodynamics (Stool Chloride Output and Concentration):

Overall Study Population: The Clinical Pharmacology Reviewer noted that in Study 37554-209, there was a significant change in stool chloride output and stool chloride concentration following four days of treatment compared to placebo (see tables below).

Table 2. Stool Chloride Output (mg/day) Change from Baseline to Day 4 (Study 37554-209)

	Crofelemer 500 mg Beads (n=26)	Placebo (n=24)
Mean (SD)	-532.4 (972.0)	-72.6 (400.2)
Median (Min, Max)	-194.2 (-3145, 525)	-113.8 (-839, 956)

(Table above is modified from the Clinical Pharmacology Review. Source is Study 37554-209 Study Report.)

Table 3. Stool Chloride Concentration (mg/g) Change from Baseline to Day 4 (Study 37554-209)

	Crofelemer 500 mg Beads (n=25)	Placebo (n=24)
Mean (SD)	-0.25 (0.56)	0.12 (0.71)
Median (Min, Max)	-0.09 (-1.51, 0.74)	0.06 (-1.29, 1.97)

(Table above is modified from the Clinical Pharmacology Review. Source is Study 37554-209 Study Report.)

Subgrouped by Race: In a Response to Information Request (received September 12, 2012), the Applicant presented results of analyses of the change from baseline in stool chloride concentrations from Study 37554-209 in subgroups defined by race (Black/African-American subjects and other subjects) (see tables below). Stool chloride output and stool chloride concentrations decreased in both African American patients treated with crofelemer relative to placebo and non-African American patients treated with crofelemer relative to placebo.

Table 4. Subgrouped by Race - Stool Chloride Output (mg/day) Change from Baseline to Day 4 (Study 37554-209)

	Black / African-American		Other	
	Crofelemer 500 mg Beads (n=3)	Placebo (n=5)	Crofelemer 500 mg Beads (n=23)	Placebo (n=19)
Mean (SD)	-1410 (1181)	-232 (226)	-418 (911)	-31 (429)
Median (Min, Max)	-1208 (-2679, -343)	-207 (-533, 71)	-106 (-3145, 525)	-60 (-839, 956)

(Table above is modified from the Response to Information Request received September 12, 2012.)

Table 5. Subgrouped by Race - Stool Chloride Concentration (mg/g) Change from Baseline to Day 4 (Study 37554-209)

	Black / African-American		Other	
	Crofelemer 500 mg Beads (n=3)	Placebo (n=5)	Crofelemer 500 mg Beads (n=22)	Placebo (n=19)
Mean (SD)	-0.9 (0.8)	-0.2 (0.72)	-0.2 (0.47)	0.9 (0.7)
Median (Min, Max)	-1.2 (-2, 0)	-0.2 (-1, 0)	-0.1 (-1, 1)	0.7 (0, 3)

(Table above is modified from the Response to Information Request received September 12, 2012.)

Both the overall results and results in subgroups defined by race (Black/African-American subjects and other subjects) will be described in the labeling (see Section 12.3 of this CDTL Review).

5.1.2 Biopharmaceutics

The reader is referred to the Biopharmaceutics Review by Mark Seggel dated August 1, 2012, for complete information. The focus of the Biopharmaceutics Review is on the dissolution method and acceptance criteria. (b) (4)

The dissolution tests and acceptance criteria initially proposed by the Applicant and those recommended by the Biopharmaceutics Reviewer are summarized below.

Initially Proposed by the Applicant:

(b) (4)

Recommendation by the Biopharmaceutics Reviewer:

Since the drug product is formulated as a delayed release (DR) tablet, the Applicant was advised to evaluate the product's performance (drug release) in accordance with "USP<711> Dissolution, Method A for Delayed-Release Dosage Forms" (test consists of an acid stage and a buffer stage). The final recommendation from the Biopharmaceutics Reviewer is summarized in the table below.

Table 6. Recommended Dissolution Method and Acceptance Criteria

Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance criteria
USP II (paddle)	75 rpm	750 ml	37°C	Acid Stage 1*: 0.1 N HCl	NMT (b) (4) at 2 hrs
USP II (paddle)	75 rpm	1000 ml	37°C	Buffer Stage 1*: Sodium phosphate buffer, pH 6.8	Q = (b) (4) at 45 minutes

*Assay by UV-spectrophotometry at 280 nm
(Table above is taken from the Biopharmaceutics Review by Mark Seggel.)

The Biopharmaceutics Reviewer noted that the Applicant agreed to the above dissolution regulatory test and acceptance criteria (written response submitted July 31, 2012). In a teleconference (July 26, 2012), the Applicant also agreed to continue to collect dissolution profiles by both the original dissolution methodology and by the new test.

The Biopharmaceutics Reviewer noted that the dissolution profiles will be submitted in a Prior Approval Supplement (PAS) to the NDA (b) (4)

5.2 Recommendation

Clinical Pharmacology: An Approval Action is the recommendation by the Clinical Pharmacology discipline. Two PMC's are recommended (see Section 13.6 of this CDTL Review.)

Biopharmaceutics: An Approval Action is the recommendation by the Biopharmaceutics discipline.

6 Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Fulyzaq (crofelemer) is not an antimicrobial agent.

7 Clinical/Statistical - Efficacy

The reader is referred to the Clinical Review by Wen-Yi Gao, and the Statistical Review by Lisa Kammerman, for complete information.

7.1 Issues

The main clinical trial reviewed in support of the proposed indication was Study NP303-101 (ADVENT) (n=376).

7.1.1 Design (NP303-101)

Study NP303-101 was a randomized, double-blind, placebo-controlled (four week) and placebo-free (twenty week), two-stage adaptive trial in HIV positive patients on stable anti-retroviral therapy (ART) with a history of diarrhea.

Key Inclusion/Exclusion Criteria

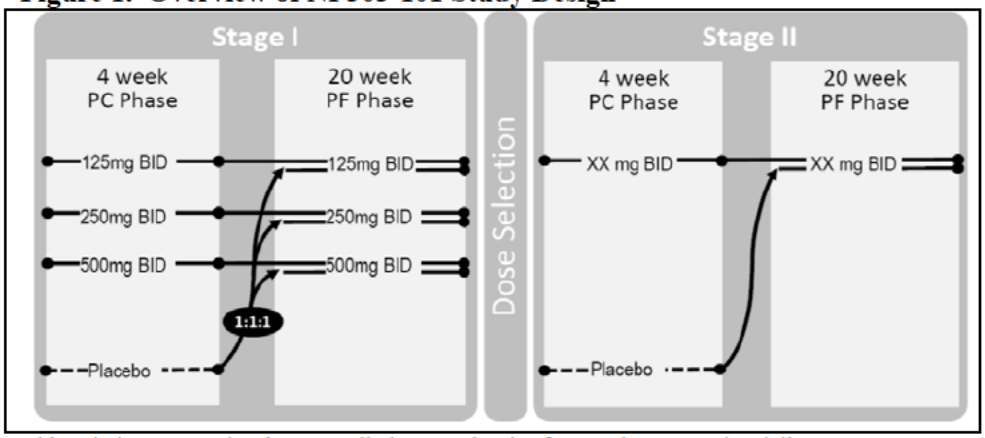
Key inclusion criteria were:
- HIV positive adults with CD4 count ≥ 100 cells/mm^3
- Stable ART regimen for ≥ 4 weeks prior to screening
- Diarrhea (for ≥ 1 month and for the month prior to screening) defined as either:
  - persistently loose stools despite regular use of anti-diarrheal medication (ADM) (e.g., loperamide, diphenoxylate, and bismuth subsalicylate) or
  - ≥1 watery bowel movements per day without regular ADM use.

Key exclusion criteria were:
- Positive gastrointestinal (GI) biopsy, GI culture, or stool test for multiple bacteria (Salmonella, Shigella, Campylobacter, Yersinia, Mycobacterium), bacterial toxin (Clostridium difficile), ova and parasites (Giardia, Entamoeba, Isospora, Cyclospora, Cryptosporidium, Microsporidium), or viruses (Cytomegalovirus).
- History of ulcerative colitis, Crohn's disease, celiac sprue, chronic pancreatitis, malabsorption, or any other GI disease associated with diarrhea.

Overview of NP303-101 Study Design

An overview of the two-stage adaptive design is provided in the figure below.

Figure 1. Overview of NP303-101 Study Design



Abbreviation: PC = placebo-controlled; PF = placebo-free; and BID = twice daily.
(Figure above is taken from the Clinical Review by Wen-Yi Gao; source is Page 39 of the Study NP303-101 Study Report.)

Each of the two stages enrolled patients separately. However, the dose for Stage II was selected based on an interim analysis of data from Stage I by an Interim Analysis Committee (see Statistical Review for more details).

Outline of Treatment Phases

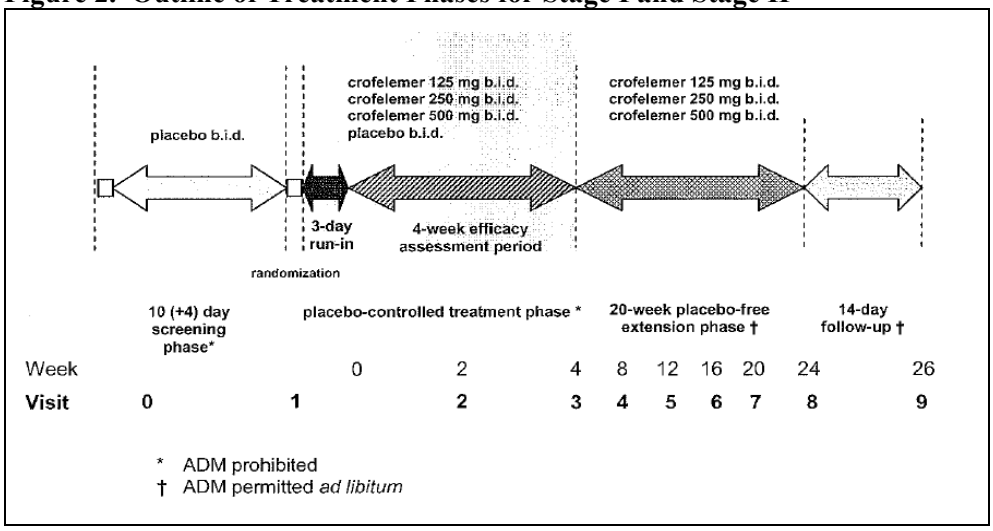
An outline of the treatment phases for Stage I and Stage II is provided in the table and figure below. Data obtained during the last 7 days of the Screening phase served as baseline for all statistical evaluations. Each stage had a 4-week double-blind Placebo-Controlled Phase (PC Phase) followed by a 20-week Placebo-Free Phase (PF Phase).

Table 7. Outline of the Treatment Phases for Stage I and Stage II

Treatment Phase (Duration)	Treatment
Screening Phase (10 days)	Placebo
PC Phase (31 days total) Run-in Period (3 days) **Assessment Period (4 weeks)**	Crofelemer or Placebo
PF Phase (20 weeks)	Crofelemer
Follow-up (14 days)	--

(Table above summarized from text in Statistics Review by Lisa Kammerman.)

Figure 2. Outline of Treatment Phases for Stage I and Stage II*



*In Stage II, only the crofelemer dose selected based on interim analysis of Stage I data and placebo bid was studied. (Figure above from Statistics Review by Lisa Kammerman; source is Page 21 of NP303-101 Protocol.)

IVRS

In both stages, diary entries were recorded daily using an Interactive Voice Response System (IVRS). Information entered into the diary during all study phases included BM frequency, consistency, urgency, fecal incontinence, abdominal pain or discomfort, use of ADM, adherence to study medication and adherence to HIV medication. Additionally, during baseline and the PC phase (but not the PF phase) opiate pain medication use was captured. See Appendix 2.

PC Phase

Entry Criteria (from Screening Phase): Only patients that met the following criteria from the Screening Phase were allowed to enter the PC Phase:

- ≥1 watery BM's per day on at least 5 of the last 7 days in the Screening Phase, and
- urgency on ≥1 of the last 7 days in the Screening Phase.

Stage I: In Stage I, patients were randomized 1:1:1:1 to one of three crofelemer dose regimens (125, 250, or 500 mg BID) or placebo.

Interim Analysis: The Statistics Reviewer noted that the Interim Analysis Committee (IAC) selected the 125 mg dose because it had the largest treatment effect of 8%, compared with 1% for 250 mg and 5% for 500 mg; however, the response rates calculated at the interim analysis differed from those used in the final analysis of the study results, resulting in an underestimate of the crofelemer 125 mg treatment at the interim analysis (8% at the interim vs. 18% for the final) (see interim analysis results used to select Stage II dose in Appendix 4, and see final analysis results in Section 7.1.2 of this CDTL Review). The Statistics Reviewer noted that two reasons accounted for this difference. First, the consulting statistician who did the interim analysis mistakenly included data from the post-randomization three-day run-in period in his calculation of response rates instead of excluding these days as stipulated in the protocol. Second, the sources of data used to define clinical non-responders differed between

the two analyses; at the interim analysis, only the daily diary data as entered into the IVRS were used to determine the use of ADM's and opiates whereas the final analysis used an additional data source (the electronic case report form). Taken together, the Statistical Reviewer noted that these two reasons changed the response rates in a way that increased the treatment effect seen for Stage I. (See Statistics Review.)

Stage II: In Stage II, patients were randomized 1:1 to crofelemer 125 mg twice daily or placebo.

Efficacy Analysis: The efficacy analysis was based on results from the PC phase of both stages (Stage I and Stage II).

Primary Efficacy Endpoint: The primary efficacy endpoint was the following:

- proportion of patients with a clinical response (defined as ≤ 2 watery BM's/ week for at least 2 of the 4 weeks during the 4-week period).

It should be noted that patients who received concomitant ADMs or opiates were counted as clinical non-responders.

Secondary Efficacy Endpoints: Secondary efficacy endpoints included the number of watery BM's 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 BM's per day, and proportion of subjects undergoing an unscheduled visit for a significant worsening or clinically significant exacerbation of diarrhea.

PF Phase

Patients treated with crofelemer in the PC phase continued the same dose in the PF phase. In Stage I, patients that received placebo in the PC phase were re-randomized 1:1:1 to one of the three crofelemer dose regimens (125, 250, or 500 mg BID) in the PF phase. In Stage II, patients that received placebo in the PC phase were treated with crofelemer 125 mg BID.

Assessments in the PF phase included weekly clinical response (defined as ≤ 2 watery BM's per week) and monthly clinical response (defined as ≤ 2 watery BM's per week during at least 2 weeks in a month).

7.1.2 Results (NP303-101 PC Phase)

Demographics and Baseline Characteristics

Demographics are summarized in the table below.

Table 8. Demographics - Placebo-Controlled Treatment Phase

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

(Table above is taken from the Statistics Review by Lisa Kammerman; Source is Table 9 of the NP303-101 Study Report.)

Baseline diarrhea characteristics are summarized in the table below.

Table 9. Baseline Diarrhea Characteristics - Placebo-Controlled Treatment Phase

	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)

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).
(Table above is taken from Wen-Yi Gao's Clinical Review. Source is Page 83 of the NP303-101 Study Report.)

Baseline HIV characteristics are summarized in the table below.

Table 10. Baseline HIV Characteristics – PC Phase

	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)

(Table above is taken from Wen-Yi Gao's Clinical Review; Source is Page 86 of the NP303-101 Study Report.)

Baseline demographic characteristics and baseline diarrhea characteristics were well-balanced across the treatment groups.

There were a numerically higher proportion of patients with CD4 count ≥ 404 in the Placebo group compared to the crofelemer treatment groups. Other baseline HIV characteristics were well-balanced across the treatment groups.

Concomitant ARTs

Concomitant antiretroviral therapies (ARTs) used in the PC Phase are shown in the table below.

Table 11. Concomitant ART Use in the PC Phase*

	125 mg BID (N = 136) n (%)	250 mg BID (N = 54) n (%)	500 mg BID (N = 46) n (%)	Placebo BID (N = 138) n (%)
Any ART	135 (99)	53 (98)	45 (98)	134 (97)
Tenofovir/Emtricitabine	45 (33)	22 (41)	16 (35)	52 (38)
Ritonavir	46 (34)	18 (33)	15 (33)	49 (36)
Lopinavir/Ritonavir	30 (22)	21 (39)	15 (33)	40 (29)
Efavirenz/Tenofovir/Emtricitabine	30 (22)	7 (13)	7 (15)	21 (15)
Tenofovir disoproxil fumarate	18 (13)	8 (15)	5 (11)	14 (10)
Antazanavir sulfate	19 (14)	3 (6)	6 (13)	22 (16)
Abacavir w/ lamivudine	17 (13)	5 (9)	5 (11)	18 (13)
Darunavir	19 (14)	4 (7)	4 (9)	14 (10)
Raltegravir	16 (12)	4 (7)	5 (11)	11 (8)
Valaciclovir hydrochloride	12 (9)	8 (15)	5 (11)	16 (12)
Fosamprenavir	12 (9)	6 (11)	4 (9)	13 (9)
Zidovudine w/ lamivudine	12 (9)	3 (6)	3 (7)	15 (11)
Lamivudine	7 (5)	6 (11)	4 (9)	6 (4)
Nevirapine	8 (6)	6 (11)	3 (7)	9 (7)
Atazanavir	5 (4)	6 (11)	2 (4)	2 (1)

* >10% of Any Treatment Group
(Table above modified from the Clinical Review by Wen-Yi Gao; source is Page 87 of the NP303-101 Study Report.)

Most patients received concomitant protease inhibitors (PI) during the PC Phase. The most frequently used ARTs in each group were tenofovir/emtricitabine, ritonavir, and lopinavir/ritonavir.

Disposition

Disposition is summarized in the table below.

Table 12. Reasons for discontinuation during the placebo-controlled treatment phase*

	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)

*Stage I and Stage II pooled together.
(Table above is taken from the Statistics Review by Lisa Kammerman; source is Table 7 of the NP303-101 Study Report.)

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

Primary Efficacy Results

The primary efficacy results are shown in the table below. The Statistics Reviewer noted that the treatment difference was 9.6% (17.6% for crofelemer vs. 8.0% for placebo) with a one-sided 97.5% confidence interval of [1.2%, ∞]. It should be noted that the p value of 0.0096 (one-sided) should be compared to a reference p value of 0.025 (because one-sided).

Table 13. Clinical Response Results for 125 mg BID and Placebo BID

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

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

Table above is taken from the Statistics Review; Source is Table 16, Clinical Study Report for NP303-101.

The observed treatment difference of 9.6% is modest. However, there is an unmet medical need for treatment of HIV associated diarrhea, particularly for patients that do not respond to other ADM's (see Section 2.1 of this CDTL Review). The Clinical Reviewer notes that the treatment difference observed in the subgroup with prior ADM use is numerically higher than that in the subgroup without prior ADM use (see Selected Exploratory Subgroup Analyses section below).

The Statistics Reviewer noted that the treatment effect differed across study stage and was statistically significant for Stage I only, despite a larger sample size in Stage II (see Clinical Response for Stage I and Stage II in Appendix 5). The Stage I treatment effect was 18% (p=.0019, one-sided) compared with 5% (p=.1690, one-sided) in Stage II. This difference was explained by the Applicant as follows: (1) Crofelemer had a more profound treatment effect in subjects with more clinically significant diarrhea; and (2) The Stage II placebo subjects had more clinically significant diarrhea as assessed by the number of watery stools at baseline than did the Stage I placebo subjects (baseline mean of 3.52 in Stage I Placebo versus 2.78 in Stage II Placebo). The Applicant asserted that the difference was likely due to the imbalance between stages in clinically significant diarrhea among the placebo-treated subjects. The Statistics Reviewer, however, noted that her review suggests that the imbalance is less pronounced and may be due to two placebo-treated subjects who had unusually high baseline values of watery stools. The Statistics Reviewer noted that among the four groups (i.e., Crofelmer 125 mg BID Stage I, Crofelmer 125 mg BID Stage II, Placebo Stage I, and Placebo Stage II), both the maximum value (15.3) and the second highest value (11.14) for Baseline Daily Watery Bowel Movements were in the Stage I placebo arm; the third highest value for Baseline Daily Watery Bowel Movements was 9.7 in the Stage II Placebo arm. (See distribution of daily watery bowel movements at baseline for Stage I and Stage II in Appendix 6.)

Secondary Efficacy Results

The secondary efficacy results are shown in the table below.

Table 14. Secondary Efficacy Endpoints –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)		

a. P-values were from an analysis of covariance (ANCOVA) model, including treatment effect and baseline as covariates.
(From Clinical Review by Wen-Yi Gao; source is Page 109 of the NP303-101 Study Report.)

Numerically greater reductions (from baseline to end of the PC phase) were observed in the crofelemer 125 mg group compared to the placebo group for each of the secondary efficacy assessments.

Selected Exploratory Subgroup Analyses

Selected exploratory subgroup analyses are summarized in the tables below.

Clinical Response by Prior ADM Use

Clinical response by prior ADM use is shown in the table below.

Table 15. Clinical Response by Prior ADM Use

Subgroup	Clinical Response		Δ
	Crofelemer 125 mg BID	Placebo	
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%

Source is Page 101 of the NP303-101 Study Report

The Clinical Reviewer noted that a numerically higher treatment difference was observed in patients receiving any prior ADM use compared to patients receiving no prior ADM use.

Other Selected Subgroup Analyses

Other selected subgroup analyses are shown in the table below.

Table 16: Other Selected Subgroup Analyses

Subgroup		Clinical Response		Δ
		Crofelemer 125 mg BID	Placebo	
Duration of Diarrhea	≤ 2 yrs	15.6% (7/45)	8.7% (4/46)	6.9%
	> 2 yrs	18.7% (17/91)	7.6% (7/92)	11.1%
Daily Watery Bowel Movements at Baseline	≤ 2	24.6% (15/61)	16.4% (9/55)	8.2%
	> 2	12.0% (9/75)	2.4% (2/83)	9.6%
Use of Protease Inhibitors	No	18.4% (9/49)	12.2% (5/41)	6.2%
	Yes	17.2% (15/87)	6.2% (6/97)	11.0%
CD4 Cell Count [cells/μL]	≥ 404	17.3% (14/81)	10.1% (10/99)	7.2%
	< 404	18.2% (10/55)	2.6% (1/39)	15.6%
Time Since HIV Diagnosed	≤ 12 yrs	14.3% (10/70)	8.8% (6/68)	5.5%
	> 12 yrs	21.2% (14/66)	7.1% (5/70)	14.1%

(Data in table above taken from Figure 8 on Page 100 of the NP303-101 Study Report.)

There appeared to be a consistent crofelemer treatment effect for clinical response (125 mg BID vs. placebo) demonstrated in subgroup analyses based on duration of diarrhea, daily watery bowel movements at baseline, use of PI, CD4 cell count, and time since HIV diagnosed.

Clinical Response by HIV Viral Load

The Applicant provided the clinical response rates in the following subgroups based on HIV viral load: HIV viral load ≥ 1000, HIV viral load 400 to 9999, HIV viral load less than 400, and HIV viral load not detectable (see table below).

Table 17. Clinical Response by HIV Viral Load

HIV Viral Load [HIV copies/mL]	Clinical Response	
	Crofelemer 125 mg BID	Placebo
≥ 1,000	0 % (0/6)	0 % (0/9)
400 to 9,999	33.3 % (2/6)	33.3 % (1/3)
< 400 (RNA detected)	0 % (0/13)	10.0 % (1/10)
< 400 (No RNA detected)	19.8 % (22/111)	7.8 % (9/116)

(Table above is taken from the Response to Information Request dated September 13, 2012.)

The number of patients in each of the subgroups with HIV viral load ≥ 1000, HIV viral load 400 to 9,999, and HIV viral load < 400 (RNA detected) was too small to determine if there is consistency of the treatment effect with HIV viral load across these subgroups and with the subgroup that included the majority of patients (HIV viral load <400 (No RNA detected)). These results will be described in the Clinical Studies section of the labeling (see Section 12.3 of this CDTL Review).

Clinical Response by Race, Gender, and Age Subgroups

Race: The statistical reviewer noted that results for the various race categories suggest that Black/African American subjects did not derive a treatment benefit from crofelemer 125 mg and that this contrasts with the finding of a consistent treatment benefit among Hispanic subjects (14.8%) and among White/Caucasian subjects (15.9%) (see table below). These results will be described in the Clinical Studies section of the labeling (see Section 12.3 of this CDTL Review).

Table 18. Clinical response rates by treatment group and race.

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

*Note: the confidence intervals are exact confidence intervals on the difference in proportions, calculated using EXACT. The analyses do not account for study stage.
(Table above is taken from Statistical Review by Lisa Kammerman; Source: Statistical Reviewer's analysis)

It should be noted that in a Response to Information Request (received September 12, 2012), the Applicant presented results of analyses of the change from baseline in stool chloride concentrations from a Phase 2 study (Study 37554-209) in subgroups defined by race (Black/African-American subjects and other subjects); there was a decrease in stool chloride concentrations in both subgroups (Black/African-American subjects and other subjects) compared to placebo (see Sections 5.1.1 and 12.3 of this CDTL Review).

Gender: The statistical reviewer noted that there were too few clinical responses (2/21 for crofelemer 125 mg and 2/22 for placebo) to conclude whether crofelemer is effective in women and whether the effect among female subjects is consistent with the effect among male subjects (see table below). These results will be described in the Clinical Studies section of the labeling (see Section 12.3 of this CDTL Review).

Table 19. Clinical Response by Gender

Gender	Crofelemer 125 mg BID	Placebo
Male	19.1% (22/115)	7.8% (9/116)
Female	9.5% (2/21)	9.1% (2/22)

(Data in table above taken from Figure 8 on Page 100 of the NP303-101 Study Report.)

Age: The statistical reviewer noted that treatment effect did not appear to differ across the two age categories (≤48 years, >48 years) that were defined by the Applicant (see table below).

Table 20. Clinical Response by Age Subgroup

Age Subgroup	Crofelemer 125 mg BID	Placebo	Δ
≤ 48 years	17.0% (16/94)	7.3% (7/96)	9.7%
>48 years	19.0% (8/42)	9.5% (4/42)	9.5%

(Data in table above taken from Figure 8 on Page 100 of the NP303-101 Study Report.)

Clinical Response by Product Lot Number

The clinical response by product lot number is summarized in the table below. Drug Product lots from the same Drug Substance Lot were pooled for the analyses.

Table 21. Clinical Response by Product Lot Number, Dose and Stage

Product Lot Number*	Stage 1			Stage 2
	125 mg	250 mg	500 mg	125 mg
3059847R	**0%** (0/2)	--	--	--
3061308R/3061703R	**14.3%** (1/7)	**7.7%** (1/13)	**16.7%** (2/12)	--
3062741R/3062743R	**23.1%** (3/13)	**7.1%** (1/14)	**0%** (0/13)	--
3063506R/3063507R	**23.1%** (3/13)	**0%** (0/13)	**41.7%** (5/12)	--
3064439R/3064440R	**22.2%** (2/9)	**10.0%** (1/10)	**28.6%** (2/7)	--
3065503R/3065505R	**0%** (0/1)	**50.0%** (2/4)	**0%** (0/2)	--
3067354R/3067355R/3067356R	--	--	--	**16.3%** (15/92)
Totals:	**20.5%** (9/44)	**9.3%** (5/54)	**19.6%** (9/46)	**16.3%** (15/92)

*Drug product lots from the same drug substance lot were pooled for the analyses.
Table above taken from Page 97 of the Summary of Clinical Efficacy.

It is difficult to determine if the clinical response is consistent across lots because the number of patients in each group (defined by Lot, Stage, and Treatment Group) is small.

7.1.3 Results (NP303-101 PF Phase)

In the placebo-free period, 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 percentages of patients that completed the placebo-free period were 84%, 73%, and 80% in the 125 mg, 250 mg, and 500 mg arms, respectively. Patients who dropped out were considered non-responders.

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

The statistical reviewer noted that at the end of the PC phase, there were a total of 46 clinical responders who continued into the PF phase (see table below); these participants include all placebo-treated subjects (n=11) who were responders at the end of the PC phase and almost all crofelemer 125 mg treated subjects (22 of 24) who were responders at the end of the PC phase.

The statistical reviewer noted that of the 22 crofelemer 125 mg responders who entered the PF phase, 14 were responders through every month of the PF phase; however, five were non-responders by Month 3. The statistical reviewer commented that based on these relatively small numbers of subjects, the results suggest a reasonable number of the crofelemer 125 mg responders maintained their response, but noted that this finding needs to be balanced by the finding that five (23%) of the subjects had lost their response to treatment by Month 3 of the PF phase.

Table 22. Durability of effect among subjects who were clinical responders at the end of the placebo-controlled (PC) phase

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

Table above is taken from the Statistics Review by Lisa Kammerman; source is the Statistical Reviewer's analysis.

7.1.4 Other Supportive Studies

There were also two other studies, Study 37554-209 (Phase 2) (n=85) and Study 37554-210 (Phase 3) (n=400) with treatment durations of 4 days and 6 days, respectively. These studies used a different formulation of crofelemer than Study NP303-101. The doses studied ranged from 500 mg to 2000 mg per day. The primary endpoint used in the two studies was change in daily stool weight.

In Study 37554-209, there was a statistically significantly higher change in stool weight in the Crofelemer 500 mg beads QID arm (n=43) compared to the placebo arm (n=42).

In Study 37554-210, there was a statistically significantly higher change in stool weight in the Crofelemer 500 mg tablets QID arm (n=100) compared to the placebo arm (n=98), but a statistically significant difference compared to placebo was not observed for the other two treatment arms, Crofelemer 250 mg tablets QID (n=102) and Crofelemer 500 mg beads QID (n=100).

Each of these studies is described in more detail in the Primary Clinical Review by Wen-Yi Gao. In addition, there is a brief description of these studies in Appendix 3 of this CDTL Review.

7.2 Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical standpoint.

8 Safety

The reader is referred to the Clinical Review by Wen-Yi Gao for complete information.

8.1 Issues

8.1.1 Exposure

The focus of the safety review is on the HIV diarrhea population. (A full listing of crofelemer clinical studies including studies in irritable bowel syndrome, traveler's diarrhea, and respiratory viral diseases is provided in Appendix 1.)

Exposure in the following two safety populations is summarized in the tables below:
- NP303-101 PC Phase
- HIV Integrated (Studies NP303-101, 37554-209, and 37554-210)

Table 23. NP303-101 PC Phase Population

Exposure Duration (Days)	Crofelemer 125 mg BID (n=136)	Crofelemer 250 mg BID (n=54)	Crofelemer 500 mg BID (n=46)	Placebo BID (N=138)
Mean (SD)	32.9 (4.6)	33.9 (2.0)	31.8 (5.5)	32.1 (5.6)
Median (Min, Max)	33.5 (1, 45)	34.0 (30, 39)	33.0 (6, 37)	33.0 (1, 42)

(Table above is modified from the Clinical Review by Wen-Yi Gao; source is Page 45 of the Summary of Clinical Safety.)

Table 24. HIV Integrated Population*

Exposure Duration (Days)	Crofelemer 250 mg daily (n=229)	Crofelemer > 250 mg daily (n=467)	Placebo (n=274)
Mean (SD)	141.4 (44.0)	47.6 (62.3)	22.1 (12.8)
Median (Min, Max)	147 (12, 185)	27 (1, 227)	28 (2, 42)

*Studies NP303-101, 37554-209, and 37554-210
(Table above is modified from the Clinical Review by Wen-Yi Gao; source is Page 47 of the Summary of Clinical Safety.)

The safety findings are presented below for each of these populations.

8.1.2 Safety Findings

NP303-101 PC Phase Population

Adverse events in the NP303-101 PC Phase Population are summarized in the table below.

Table 25. Summary of Adverse Events (NP303-101 PC Phase)

Subjects with AE's	Crofelemer 125 mg BID (n=130)	Crofelemer 250 mg BID (n=54)	Crofelemer 500 mg BID (n=42)	Placebo BID (N=137)
Any AE's	45 (34.6%)	10 (18.5%)	7 (16.7%)	45 (32.8%)
Severe	2 (1.5%)	1 (1.9%)	0	5 (3.6%)
Moderate	16 (12.3%)	6 (11.1%)	2 (4.8%)	16 (11.7%)
Mild	27 (20.8%)	3 (5.6%)	5 (11.9%)	24 (17.5%)
Drug-related AE's	9 (6.9%)	2 (3.7%)	2 (4.8%)	5 (3.6%)
Deaths	0	0	0	1 (0.7%)
Non-Fatal SAE's	2 (1.5%)	0	0	4 (2.9%)
Discontinued due to AE's	0	0	0	4 (2.9%)

(Table above is modified from the Clinical Review by Wen-Yi Gao; source is Page 55 of the Summary of Clinical Safety.)

Two (1.5%) patients in the Crofelemer 125 mg BID group, one (1.9%) patients in the Crofelemer 250 mg BID group, and 5 (3.6%) patients in the Placebo group reported AE's indicated as severe in intensity.

No patient treated with crofelemer died during the PC phase of NP303-101.

Non-fatal SAE's were reported for 2 (1.5%) patients in the Crofelemer 125 mg BID group and 4 (2.9%) patients in the Placebo group. The two SAE's in the Crofelemer 125 mg BID group were Escherichia sepsis and pneumonia. The Escherichia sepsis case occurred in a 41 year old male at Day 7 of the PC phase; the event resolved three days later following hospitalization and IV antibiotics, and the patient continued into the PF phase. The pneumonia case occurred in a 59 year old male at Day 21 of the PC phase; following hospitalization for seven days, the event was considered resolved, and the patient continued into the PF phase. The Clinical Reviewer commented that he agreed with the Investigator's assessment that neither case was related to crofelemer treatment.

Four (2.9%) patients in the Placebo group discontinued prematurely due to AE's, and no patients discontinued prematurely due to AE's in the crofelemer arms.

Drug-related AE's are described in the Clinical Review. However, no specific safety concerns are evident from this data.

In addition, it should be noted that no clear association of incidence of AE's with dose was appreciated from this data.

HIV Integrated Population

Adverse events in the HIV Integrated Population are summarized in the table below.

Table 26. Summary of Adverse Events (HIV Integrated Population)

Subjects with AE's	Crofelemer 250 mg daily (n=229)	Crofelemer > 250 mg daily (n=467)	Placebo (n=274)
Any AE's	145 (63.3%)	238 (51.0%)	100 (36.5%)
Severe	13 (5.7)	16 (3.4)	10 (3.6)
Moderate	69 (30.1)	80 (17.1)	34 (12.4)
Mild	63 (27.5)	142 (30.4)	56 (20.4)
Drug-related AE's	27 (11.1)	107 (22.9)	34 (12.4)
Deaths	1 (0.4)	0	1 (0.4)
Non-Fatal SAE's	11 (4.8)	8 (1.7)	6 (2.2)
Discontinued due to AE's	5 (2.2)	10 (2.1)	7 (2.6)

(Table above is modified from the Clinical Review by Wen-Yi Gao; source is Page 57 of the Summary of Clinical Safety.)

Thirteen (5.7%) patients in the Crofelemer 250 mg daily group, sixteen (3.4%) patients in the Crofelemer > 250 mg daily group, and ten (3.6%) patients in the Placebo group reported AE's indicated as severe in intensity.

There was one death recorded in a patient receiving crofelemer. This death was deemed to be unrelated to crofelemer treatment (see Clinical Review). This patient was a 62 year old male with a history of HIV, hypertension, coronary artery disease, renal insufficiency, and chronic bronchitis secondary to a long history of smoking. He died due to cardiac arrest at Visit 5 (Week 12) of Study NP303-101; he was receiving Crofelemer 125 mg BID.

Non-fatal SAE's were reported for 11 (4.8%) patients in the Crofelemer 250 mg daily group, eight (1.7%) patients in the Crofelemer >250 mg daily group, and for six (2.2%) patients in the Placebo group.

Of the 11 patients that experienced SAEs in the Crofelemer 250 mg daily group, two were already discussed previously (the patient with Escherichia sepsis and the patient with pneumonia). One patient experienced three SAE's (suicide attempt, cellulitis, and suicidal ideation). The remaining eight SAE cases were as follows: suicide attempt, tracheobronchitis, appendicitis, syncope, hemorrhagic gastritis, radius fracture, viral gastroenteritis, and prostate cancer. The Clinical Reviewer noted that the two patients with an SAE of suicide attempt each had a medical history significant for depression, anxiety, and other psychiatric conditions. All the SAE's resolved except prostate cancer and radius fracture.

Of the eight patients that experienced SAEs in the Crofelemer > 250 mg daily group, four patients each experienced more than one SAE as follows: (1) One patient experienced two episodes of depression; (2) the second patient experienced anemia, depression, Pneumocystis jiroveci pneumonia, and rectal ulcer; (3) The third patient experienced pneumonia and hypotension; and (4) The fourth patient experienced disorientation, dysarthria, and

hallucination. The remaining four SAE cases were as follows: embolic stroke, gastroenteritis, anemia, and dyspnea. It should be noted that the patient that experienced disorientation, dysarthria, and hallucination had a history of bipolar disorder, panic attacks, cluster seizures, and encephalopathy. Also, the patient that experienced two episodes of depression had a history of depression.

The Clinical Reviewer commented that there is not sufficient evidence to support a causal relationship between the non-fatal SAEs in the HIV Positive Integrated Safety Population and the study drug.

Five (2.2%), 10 (2.1%), and 7 (2.6%) patients in the Crofelemer 250 mg daily group, Crofelemer > 250 mg daily group, and Placebo group, respectively, discontinued prematurely due to AE's.

Drug-related AE's are described in the Clinical Review. However, no specific safety concerns are evident from this data.

In addition, it should be noted that no clear association of incidence of AE's with dose was appreciated from this data.

AE's occurring in ≥ 2% of patients in the Crofelemer 125 mg BID group at a higher frequency than the placebo arm are summarized in the table below; only the Crofelemer 125 mg BID and the Placebo arms are shown.

Table 27. Adverse Events Occurring in ≥ 2% of Patients in the 125 mg BID Group

System Organ Class Adverse Reaction	Crofelemer 125 mg BID N = 229 n (%)	Placebo N = 274 n (%)
Infections and Infestations		
Upper respiratory tract infection	13 (5.7%)	4 (1.5%)
Bronchitis	9 (3.9%)	0
Urinary tract infection	5 (2.2%)	2 (0.7%)
Nasopharyngitis	5 (2.2%)	2 (0.7%)
Giardiasis	5 (2.2%)	0
Gastrointestinal Disorders		
Flatulence	7 (3.1%)	3 (1.1%)
Nausea	6 (2.6%)	4 (1.5%)
Hemorrhoids	5 (2.2%)	0
Abdominal distension	5 (2.2%)	1 (0.4%)
Investigations		
Increased bilirubin	7 (3.1%)	3 (1.1%)
Increased alanine aminotransferase	5 (2.2%)	3 (1.1%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	6 (2.6%)	4 (1.5%)
Arthralgia	6 (2.6%)	0
Musculoskeletal pain	5 (2.2%)	1 (0.4%)
Psychiatric Disorders		
Anxiety	5 (2.2%)	1 (0.4%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	8 (3.5%)	3 (1.1%)

(Table above is modified from Table 9 of the Summary of Clinical Safety, Page 68.)

For the Crofelemer 125 mg BID group, the most common AE's in the Infections and Infestations SOC (in decreasing order of frequency) were upper respiratory tract infection, bronchitis, urinary tract infection, nasopharyngitis, and giardiasis. In the Gastrointestinal Disorders SOC, the most common AE's were flatulence, nausea, hemorrhoids, and abdominal distension. In the Investigations SOC, the most common AE's were increased bilirubin and increased alanine aminotransferase. In the Musculoskeletal and Connective Tissue Disorders SOC, the most common AE's were back pain, arthralgia, and musculoskeletal pain. In the Psychiatric disorder SOC the most common AE was anxiety, and in the Respiratory, Thoracic and Mediastinal Disorders SOC the most common AE was cough.

8.2 Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

9 Advisory Committee Meeting

This application was not presented to an Advisory Committee.

However, this application was presented at a Center Director Briefing on August 6, 2012.

Following an introduction by Dr. Julie Beitz (Director, ODE III), the following presentations were given:

- Clinical Presentation by Dr. Wen-Yi Gao (Primary Clinical Reviewer, DGIEP)
- ONDQA Presentation by Dr. Terrance Ocheltree (Director, DNDQA II)
- Botanical Review Team Presentation by Dr. Shaw Chen (Team Leader, BRT, ODE II)

The main issue was the adequacy of the product characterization from both the ONDQA and botanical perspectives.

The Clinical Presentation was primarily for background. It provided a brief summary of the unmet medical need for the treatment of HIV associated diarrhea, and an overview of the efficacy and safety results from Study NP303-101. The Clinical Reviewer included a slide showing the proportion of patients that achieved the primary endpoint by product lot; he concluded that compelling trends were not identified, although the number of patients in each group (defined by lot, stage, and treatment group) was small.

The ONDQA presentation focused on the ONDQA determination that sufficient information to assure the identity of the drug product has not been provided by the applicant in accordance with 21 CFR 314.125(b)(1).

The BRT presentation focused on the BRT determination that there is adequate assurance of the therapeutic consistency of future marketing batches based on a schema that includes a Pre-CMC assessment (relying on plant biology and process controls) and a Post-CMC assessment (relying on mechanism of action studies, widespread use, and the lack of an observed difference in efficacy across lots in the Phase 3 studies) in addition to a conventional CMC assessment (relying on analytical chemistry and process control).

The key questions for the Center Director were the following (taken from the last slide in the presentation):

- Is this NDA approvable?
- If no, what additional information should the Applicant provide to support approval?
- If yes, what post-marketing studies should be conducted?

The Center Director Recommendations (taken from the Minutes of the Center Director Briefing) were the following:

- Dr. Woodcock believes that the application is approvable and further CMC characterization is not needed at this time, provided that the applicant implements a potency bioassay to test commercial batches prior to release.
- It was undecided whether further CMC data would be required post-approval.

The following was also noted in the minutes of the Center Director Briefing:

- Dr. Beitz will make the decision on this NDA application. If there is an internal dispute regarding the decision, the matter will be brought to Dr. Woodcock under the Center's usual appeal process.

10 Pediatrics

The application was presented to the Pediatric Research Committee (PeRC) on July 25, 2012.

The Division presented a partial waiver in patients birth to 4 weeks of age because no approved anti-retroviral therapy is available in patients below 4 weeks of age. A deferral was also presented in pediatric patients 1 month to 17 years of age for the treatment of HIV-associated diarrhea.

(b) (4) the Division believed that this product should be waived for use in neonates. Antiviral therapy is part of the etiology that causes diarrhea in HIV patients, infectious diarrhea and sarcoma diarrhea (at least 4 types of diarrhea). Another product is currently approved for use in the treatment of diarrhea in patients down to 14 days old.

The pediatric plan for this product is to evaluate PK, efficacy and safety for several different doses over a four week period. (b) (4)

The PeRC agreed with the Division to grant a partial waiver in patients birth to one month because studies would be impossible or highly impractical because the clinical endpoints in the lowest age group would be impossible to meet because very few infants are treated with HIV medications. The deferral was also agreed to by the PeRC for those patients 1 month through 17 years because the product is ready for approval in adults.

The PeRC recommended that the Division examine the possibility that it may need additional safety information in animal models in order to define toxicities. The nonclinical data from juvenile animals is summarized in Section 4.1 of this CDTL Review; the Nonclinical Reviewer noted that there were no significant treatment-related clinical signs in F1 pups during the preweaning period. In F1 pups surviving to scheduled necropsy, clinical signs were similar across all dose groups including controls and low in incidence. Upon initiating pediatric studies, the Division will consider if a larger safety study is also needed for this product.

The PeRC also recommended that the Division consider (b) (4)

11 Other Relevant Regulatory Issues

11.1 QT Evaluation

In vitro Results

In vitro, crofelemer produced dose-dependent inhibition of hERG (human ether-a-go-go) K^+ current. The Nonclinical Reviewer noted that because of its low oral bioavailability, the potential risk of QT prolongation due to <2% free crofelemer is likely minimal to none (see Section 4.1 of this CDTL Review).

Waiver Request

(b) (4) The QT-IRT Reviewer noted the following:

(1) Crofelemer inhibited hERG currents in a concentration-dependent manner, and the IC50 is > 100-fold the clinical Cmax exposure;
(2) Following the therapeutic dose of 125 mg BID, the detected crofelemer Cmax is 72 ng/mL. Given the median molecular weight of 2,100 Daltons, the estimated concentration is 34 nM, high enough to be concerned about possible ion channel effects.
(3) There were insufficient number of EKG's in the two studies reported by the Applicant, Study CFFE1091 (food effect study in 23 patients) and Study NP303-101 (50 patients received the 500 mg BID dose). No large effects on QTcF were reported, but small effects on QTc cannot be ruled out because the studies were not designed to exclude ≤10 ms effects.

(See Consult Review by Monica Fiszman dated September 28, 2011 for complete information.) (b) (4) A letter was sent to the Applicant on October 7, 2011 stating that a TQT assessment should be conducted.

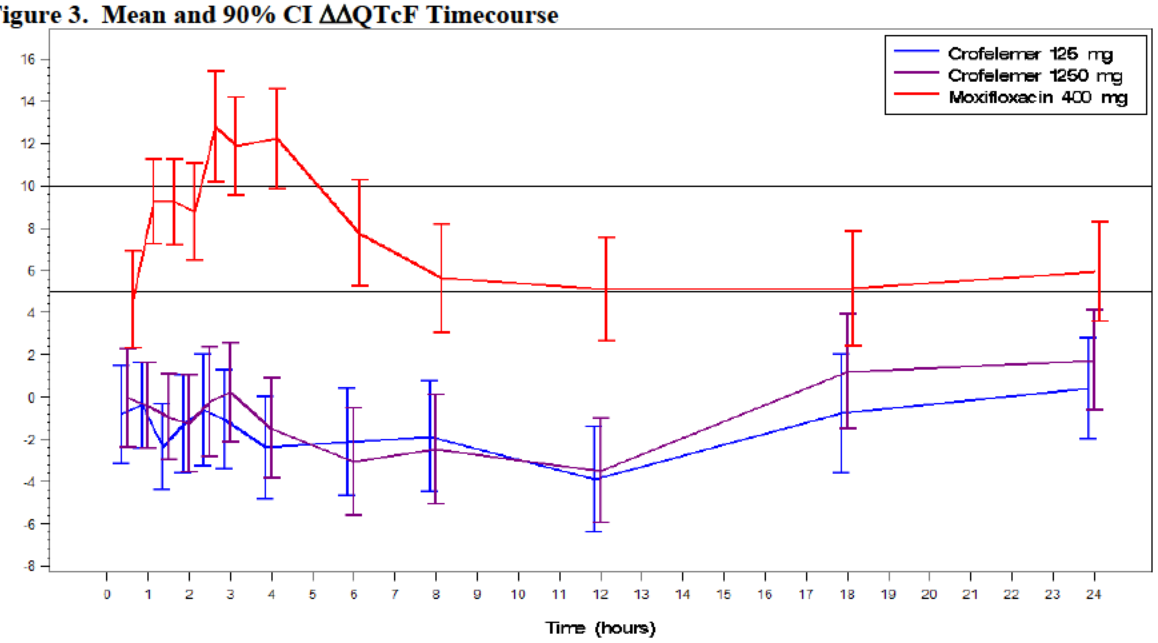
TQT Study

Protocol: The sponsor submitted a protocol for the required Thorough QT (TQT) study (Study CFQT1092) entitled "Evaluation of the Effect of Therapeutic and Supratherapeutic Single-Dose Crofelemer on the QT/QTc Intervals in Healthy Volunteers," on November 7, 2011. A consult was requested from the QT-IRT team to review the protocol on November 7, 2011. The QT-IRT Reviewer had a number of recommendations (see Consult Review by Monica Fiszman dated January 10, 2012 for complete information). These recommendations were communicated to the Applicant in a letter dated January 11, 2012.

Results: The TQT study was completed, and the Applicant submitted the TQT Study Report to the IND on August 22, 2012. The QT-IRT Team was consulted to review the TQT Study Report (see Consult Review by Janice Brodsky dated October 23, 2012 for complete information). The QT-IRT Reviewer noted the following results:

- The largest upper bounds of the 2-sided 90% CI for the mean difference between crofelemer and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.
- The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in the figure below, indicating that assay sensitivity was established. The figure below displays the time profile of ΔΔQTcF for different treatment groups.

Figure 3. Mean and 90% CI ΔΔQTcF Timecourse



All CIs are unadjusted, including moxifloxacin.

(The figure above is taken from Page 13 of the QT-IRT Review by Janice Brodsky dated October 23, 2012.)

In this randomized, blinded, four-period crossover study, 48 healthy subjects received crofelemer, placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary of findings is presented in the table below.

Table 28. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Crofelemer and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hr)	ΔΔQTcF (ms)	90% CI (ms)
Crofelemer 125 mg	24	0.4	(-2.0, 2.8)
Crofelemer 1250 mg	24	1.7	(-0.6, 4.1)
Moxifloxacin 400 mg*	2.5	12.8	(10.2, 15.4)

Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 9.2 ms.

(The table above is taken from Page 2 of the QT-IRT Review by Janice Brodsky dated October 23, 2012.)

Conclusion: The QT-IRT Reviewer concluded that no significant QTc prolongation effect of crofelemer was detected in this TQT study.

11.2 Office of Scientific Investigations (OSI) Audits

The reader is referred to the OSI Clinical Inspection Summary by Khairy Malek, dated August 9, 2012 for complete information. The three site inspections are summarized in the table below.

Table 29. Overview of Sites Inspected (Study NP303-101)

Site Number/ Investigator/ Location	Number of Patients*	Inspector's Key Findings
Site #60 Michael Wohlfeiler, M.D. Miami Beach, FL	9	• Few protocol violations: – One subject did not have the screening ECG until V1 and the tracing was not reviewed until the day after dosing. – Protocol-specified physical examination of the rectum, lymph nodes, genitourinary system/gynecological organs was not conducted for any subject. – There was a failure to question four subjects at one or two visits about adverse reactions and concomitant medications. • Study records availability – Study records were considered incomplete as copies of the original IVRS diary entries were not available at the site; the Sponsor provided printouts while the audit was ongoing. – During the inspection of the Sponsor (Salix), the original entries from the patients were compared to the line listings and found to be consistent.
Site #45 Michael Somero, M.D. Palm Springs, CA	7	• Inadequate informed consent – four enrolled subjects did not sign the most recent version of the informed consent document • A protocol violation – One subject was enrolled before obtaining a protocol required urine test for opiates. • Study records availability – The site had printouts, not the original IVRS diary entry responses of the subjects. – These originals were inspected during the inspection of the Sponsor.
Site #11 Patrick Clay, Pharm.D.	6	• Study records availability – Copies of the original entries of the patients' diaries in the IVRS were not available at the site • Inaccurate records – There were minor discrepancies between the subjects' charts and the eCRFs. Examples of these minor discrepancies included categorization of relatedness and severity of AEs and whether the AE resolved or was still ongoing.

*Number of patients that completed the study.

In addition to the above clinical sites, the field investigator audited Protocol NP303-101 at the Sponsor's site.

Inspection of the three clinical sites (Drs. Wohlfeiler, Somero and Clay) noted record keeping deficiencies that were systemic to the study because the Sponsor did not provide each investigator with the IVRS data at the close of the study. However, this data could be verified at the Sponsor site.

The OSI Clinical Inspection Summary notes that the inspection of Salix Pharmaceuticals, Inc. was classified as NAI because failure to provide copies of the original patient diary IVRS entries is not considered a regulatory violation by the sponsor under the FDA regulations concerning sponsor responsibilities [21CFR 312.50 to 312.59].

Because the additional minor violations at each of the three clinical sites did not affect the validity of the data, the overall assessment of the inspector from the inspection of the three clinical sites was that the data are reliable and can be used in support of the NDA.

12 Labeling

12.1 Proprietary Name

For complete information, see the DMEPA Proprietary Name Review by Manizheh Siahpoushan dated March 9, 2012, and DMEPA Proprietary Name Review by Anne Crandall Tobenkin and Lubna Merchant dated September 5, 2012.

The initially proposed proprietary name was (b) (4). The Division of Medication Errors and Prevention Analysis (DMEPA) concurred with the findings of OPDP's promotional assessment of the proposed name (see Section 12.2 below).

Although the proposed proprietary name was deemed acceptable by the DMEPA Proprietary Name Reviewer from a promotional perspective, it was not deemed acceptable from a safety perspective. The DMEPA Proprietary Name Reviewer noted that the proposed name is vulnerable to name confusion with (b) (4). The decision to deny the name was communicated to the Applicant in a Proprietary Name Denied Letter dated March 20, 2012.

The Applicant proposed the proprietary name (b) (4) in a request submitted May 1, 2012. DMEPA notified the Applicant in a teleconference on May 31, 2012, that the proposed proprietary name is problematic from a medication error perspective because (b) (4) The Applicant submitted a request dated June 27, 2012, that the proposed proprietary name (b) (4) be withdrawn from review.

The Applicant proposed the proprietary name (b) (4) and provided for consideration two alternate names, Fulyzaq and (b) (4), in a request submitted August 1, 2012. In a teleconference with the Applicant on August 23, 2012, the DMEPA Reviewers explained to the Applicant that there are safety concerns with the proposed name (b) (4) Specifically, (b) (4) has orthographic similarities with (b) (4) and is thus vulnerable to name confusion.

In a request submitted August 24, 2012, the Applicant proposed the proprietary name (b) (4) and withdrawal of the previously proposed proprietary name (b) (4)

In a request submitted August 27, 2012, the Applicant proposed the proprietary name Fulyzaq and withdrawal of the previously proposed proprietary name (b) (4)

DMEPA concluded that the proprietary name of "Fulyzaq" was acceptable. See the DMEPA Proprietary Name Review by Lubna Merchant dated September 5, 2012, for complete information.

12.2 Office of Prescription Drug Promotion (OPDP) Comments

The Office of Prescription Drug Promotion (OPDP) determined the initially proposed name (b) (4) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Manizheh Siahpoushan dated March 9, 2012.

OPDP also determined that the final proposed name (Fulyzaq) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Lubna Merchant dated September 5, 2012.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The main revisions to the Applicant's proposed Physician Labeling are summarized below:

- Indications and Usage (Section 1 of Label): The Applicant's originally proposed wording "for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy" was revised to remove the "control" term and to add "non-infectious" before diarrhea.
- Warnings and Precautions (Section 5 of Label): The following statement was added: "If infectious etiologies are not considered, and BRAND NAME (crofelemer) is initiated based on a presumptive diagnosis of non-infectious diarrhea, then there is a risk that patients with infectious etiologies will not receive the appropriate treatments, and their disease may worsen. Before starting BRAND NAME (crofelemer), rule out infectious etiologies of diarrhea." (The Applicant had initially proposed "(b) (4)
- Pharmacodynamics (Section 12.2 of Label): The following statement was added:
  - "Consistent with the mechanism of action of crofelemer (i.e., inhibition of CFTR and CaCC in the GI lumen), data suggest stool chloride concentrations decreased in patients treated with FULYZAQ (500 mg four times daily) (n=26) for four days relative to placebo (n=24); stool chloride concentrations decreased in both African American patients treated with FULYZAQ (n=3) relative to placebo (n=5) and non-African American patients treated with FULYZAQ (n=23) relative to placebo (n=19)."

- Clinical Studies (Section 14 of Label): The following statements were added:
  - "There were too few female subjects and subjects with an HIV viral load > 400 copies/mL to adequately assess differences in effects in these populations."
  - "Among race subgroups, there were no differences in the consistency of the crofelemer treatment effect except for the subgroup of African-Americans; crofelemer was less effective in African-Americans than non-African-Americans."

In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from the Division of Prescription Drug Promotion (DPDP) and the Study Endpoints and Labeling Development (SEALD) Team.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. They made a number of recommendations that were communicated to the Applicant on July 25, 2012 (see DMEPA Label and Labeling Review by Manizheh Siahpoushan dated March 1, 2012).

13 Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The Primary Clinical Reviewer and Primary Statistical Reviewer each recommend an Approval action.

The CMC/Botanical/Bioassay Reviewers' recommendations are as follows:

- CMC: Although the First Primary CMC Review noted that there were deficiencies identified in the NDA that preclude approval of this application, the Second Primary CMC Review noted that those deficiencies had been resolved and recommends approval.
- Botanical: Both the primary and secondary Botanical Reviews recommend approval.
- Bioassay: The Bioassay Reviewers recommend approval of the cell-based assay for crofelemer, pending a favorable inspection of the testing facility and a favorable recommendation from the Office of Compliance.

This Reviewer concurs with the above recommendations.

13.2 Risk Benefit Assessment

The benefit of crofelemer in HIV-associated diarrhea has been established in the clinical trials. There is currently no treatment specifically approved for HIV-associated diarrhea particularly for patients who have tried other ADMs not specifically approved for this condition. The safety profile was acceptable based on what was found in the clinical trials. One key risk was identified. If crofelemer is initiated in patients based on a presumptive diagnosis of non-infectious diarrhea, then there is a risk that patients with infectious etiologies will not receive the appropriate treatments, and their disease may worsen; this risk has been addressed through labeling (statement in the Warnings and Precautions section).

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Postmarketing required pediatric studies under PREA are recommended for the current efficacy supplement application, with the following language for the Approval Letter:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 30 days because necessary studies are impossible or highly impracticable as very few patients below 30 days of age are treated with anti-retroviral therapy.

We are deferring submission of your pediatric study for ages 1 month to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

> A pediatric study to evaluate pharmacokinetics (PK), efficacy for symptomatic relief of non-infectious diarrhea, and safety with different doses of crofelemer over a four week period in HIV-positive pediatric patients, ages 1 month to 17 years of age, on anti-retroviral therapy.
>
> Final Protocol Submission: 06/2013
> Study/Trial Completion: 06/2017
> Final Report Submission: 12/2017

Submit the protocol to your IND 051818 with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

The postmarketing requirements below are recommended:

Pharmacology/Toxicology:

Pharm/Tox PMR #1: A 6-month rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

SPA Submission:	10/2013
Final Protocol Submission:	01/2014
Study Completion:	12/2014
Final Report Submission:	06/2015

Pharm/Tox PMR #2: A 2-year rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

SPA Submission:	12/2013
Final Protocol Submission:	04/2014
Study Completion:	10/2016
Final Report Submission:	06/2017

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The postmarketing commitments below are recommended:

Clinical Pharmacology:

CP PMC#1: An *in vitro* study to determine whether crofelemer is an inhibitor of the transporters p-glycoprotein and BCRP.

Final Protocol Submission:	03/2013
Study/Trial Completion:	09/2013
Final Report Submission:	03/2014

CP PMC#2: An *in vivo* study in human subjects to evaluate whether crofelemer inhibits CYP 3A4 using a probe that is a pure substrate of CYP 3A4.

Final Protocol Submission: 06/2013
Study/Trial Completion: 12/2013
Final Report Submission: 06/2014

CMC:

CMC PMC #1: An elemental analysis to identify the source and identity of potential (b) (4) in crofelemer.

Final Report Submission: 12/2013

CMC PMC #2: Characterize (b) (4) crofelemer (b) (4)

Final Report Submission: 12/2013

CMC PMC #3: Revise the current HPLC methods for assay and related substances for the drug substance and drug product or develop new methods. The revised or new methods must be stability indicating and appropriately validated.

Final Report Submission: 12/2013

Bioassay:

Bioassay PMC #1: Re-evaluate the specification and revise as needed for the crofemeler cell-based assay that uses (b) (4) after one year of product lots of crofelemer (anticipated to be (b) (4) lots) have been manufactured.

Final Report Submission: 2/2014

Bioassay PMC #2: To validate and implement the cell-based potency assay that uses (b) (4)

Final Report Submission: 1/2014

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: List of Crofelemer Clinical Studies

A full listing of crofelemer clinical studies is provided below. The total safety database includes more than 1,800 subjects.

Diarrhea

Studies included 1,699 patients with diarrhea (Diarrhea in HIV+ Individuals, Diarrhea Predominant-Irritable Bowel Syndrome, Traveler's Diarrhea, Non-Specific Diarrhea, or Acute Infectious Diarrhea) and 70 healthy subjects. In these trials, crofelemer was administered as enteric coated beads or tablets.

Table 30. Clinical Trials with Crofelemer for Diarrhea

Trial No. Year Completed	Phase	Trial Design	Crofelemer Formulation	Treatment Groups: No. Subjects	Treatment Duration
Pharmacokinetic Trials					
51818-101 1996	1	Single-Dose, Open-Label PK in Healthy Adult Males	Enteric Coated Beads	Crofelemer 1250 mg n = 6	Single Dose
51818-102 1997	1	Open-Label, Single and Multiple Dose PK in Healthy Adult Males	Crofelemer Tablets	Part 1: Crofelemer 1250 mg Single Dose Part 2: Crofelemer 500 mg Q6H for 48 hours n = 8	48 Hours
37554-103 1998	1	Double-Blind, Placebo-Controlled Crossover PK Drug Interaction (Zidovudine, Lamivudine and Nelfinavir) Trial in Healthy Adults	Crofelemer Tablets	Crofelemer 500 mg Q6H for 5 days (Placebo crossover) n = 28	5 Days
CFFE1091 2010	1	Food Effect Trial: Single Dose Fed/Fasted Crossover in Healthy Adults	Crofelemer Tablets	Crofelemer 500 mg n = 28	Single Dose
HIV/AIDS Associated Diarrhea					
CFHD3092 **ongoing**	3	Open-label, safety and tolerability evaluation	Tablets	Crofelmer 125 mg BID; current enrollment (as of 15 Sep 2011) = 182	48 weeks
ADVENT 2011	3	Randomized, Double-Blind, Parallel Group, Placebo-Controlled, 2-Stage, Adaptive Trial Design	Tablets	Crofelemer 125 mg BID: PC=136 / PF=220 Crofelemer 250 mg BID: PC=54 / PF=67 Crofelemer 500 mg BID: PC=46 / PF=50 Placebo BID: PC=138 / PF=0	4 Weeks / 20 Weeks
37554-210 1998	3	Double-Blind, Randomized, Placebo-Controlled	Enteric Coated Beads; Tablets	Crofelemer 250 mg tablets Q6H: 102 Crofelemer 500 mg tablets Q6H: 100 Crofelemer 500 mg beads Q6H for 6 days followed by 500 mg tablets Q6H for up to 27 days: 100 Placebo: 98	27 Days
37554-209 1997	2	Double-Blind, Randomized, Placebo-Controlled	Enteric Coated Beads	Crofelemer 500 mg Q6H: 43 Placebo Q6H: 42	4 Days
Diarrhea-Predominant Irritable Bowel Syndrome					
TRN-002-201 2005	2	Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging (Males and Females)	Tablets	Crofelemer 125 mg BID: 62 Crofelemer 250 mg BID: 60 Crofelemer 500 mg BID: 62 Placebo BID: 61	12 Weeks
TRN-002-202 2007	2	Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging (Females)	Tablets	Crofelemer 125 mg BID: 120 Placebo BID: 120	12 Weeks

APPENDIX 1 (cont.): List of Crofelemer Clinical Studies (cont.)

Travelers' Diarrhea / Non-Specific Diarrhea					
SP-303-II-08b 1996	2	Open-Label Pilot (Mexico)	Enteric Coated Beads	Crofelemer 1250 mg loading dose followed by 250 mg Q6H for 24 hours then 500 mg Q6H for 24 hours: 43 Crofelemer 500 mg Q6H: 16 Crofelemer 250 mg Q6H: 16	48 Hours
51818-201 1997	2	Double-Blind, Randomized, Placebo-Controlled (Mexico)	Tablets	Crofelemer 50 mg Q6H: 30 Crofelemer Q6H: 31 Placebo: 31	48 Hours
51818-202A 1997	2	Double-Blind, Randomized, Placebo-Controlled (Mexico)	Enteric Coated Beads; Tablets	Crofelemer Tablets 250 mg Q6H: 57 Crofelemer Tablets 500 mg Q6H: 57 Crofelemer Beads: Q6H: 58 Placebo Q6H: 54	48 Hours
51818-602 1998	2	Double-Blind, Randomized, Placebo-Controlled (Venezuela)	Tablets	Crofelemer 125 mg Q6H: 36 Crofelemer 250 mg Q6H: 34 Crofelemer 500 mg Q6H: 35 Placebo Q6H: 35	48 Hours
51818-900 1998	2	Double-Blind, Randomized, Placebo-Controlled (Mexico and Jamaica)	Tablets	Crofelemer 125 mg Q6H: 46 Crofelemer 250 mg Q6H: 48 Crofelemer 500 mg Q6H: 46 Placebo Q6H: 44	48 Hours
Acute Infectious Diarrhea					
C002 2010	2	Multicenter, Randomized, Double-Blind, Placebo-Controlled	Tablets	Crofelemer 125mg Q12H: 44 Crofelemer 250mg Q12H: 46 Crofelemer 500mg Q12H: 39 Placebo Q12H: 43	3 days

Abbreviations: ADVENT = Anti-Diarrhea therapy in HIV disease – EmergiNg Treatment concepts (Trial NP303-101); BID = twice daily; HIV/AIDS = human immunodeficiency virus/ acquired immunodeficiency syndrome; PC = placebo-controlled phase; PF = placebo-free phase; PK = pharmacokinetics; Q6H = every 6 hours.

APPENDIX 1 (cont.): List of Crofelemer Clinical Studies (cont.)

(b) (4)

APPENDIX 2: Interactive Voice Response System

Information recorded daily using an IVRS is shown in the figures below.

Figure 4. Information recorded daily during all study phases, using an IVRS

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

Above taken from Statistics Review by Lisa Kammerman; source is the NP303-101 Clinical Study Report, Section 9.5.2.1.

Figure 5. Information recorded daily during baseline and the placebo-controlled treatment phase, using an IVRS

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

Above taken from Statistics Review by Lisa Kammerman; source is the NP303-101 Clinical Study Report, Section 9.5.2.1.

APPENDIX 3: Studies 37554-209 and 37554-210

A brief description of Studies 37554-209 and 37554-210 is provided below. More details can be found in the Primary Clinical Review by Wen-Yi Gao.

Study 37554-209 (Phase 2)

Key design features are summarized in the table below.

Table 32. Key Design Features – Study 37554-209

N (total):	▪ 85
Year Conducted:	▪ 1997
Key Selection Criteria:	▪ HIV adults ▪ Stool weight > 200 g ▪ ≥ 3 abnormal BM's (soft or watery) within 24 hours before receiving the first dose and while not taking anti-diarrheal medications
Arms:	▪ Crofelemer 500 mg* QID X 4 days (n=43) ▪ Placebo (n=42)
Primary Endpoint Definition	▪ Change from baseline in daily stool weight

*beads in capsules

Primary efficacy results are summarized in the table below.

Table 33. Stool Weight: Primary Analysis – ITT Population (Study 37554-209)

Inpatient Period	Crofelemer 500 mg beads n=43	Placebo n=42
Stool Weight at Baseline (g)		
Mean (SD)	861.3 (604.67)	730.9 (720.14)
Median	707.7	547.0
Min, Max	220, 3407	206, 4701
P-value (vs. placebo)[a,b]	0.3074	--
Categories of stool weight at baseline, n (%)		
Low (≤ 740 g)	24 (55.8)	28 (66.7)
High (> 740 g)	19 (44.2)	14 (33.3)
P-value (vs. placebo)[a,b]	0.2725	--
Change: Baseline to Day 4 (g)		
Mean (SD)	-401.3 (531.65)	-192.4 (381.57)
Median	-267.5	-232.8
Min, Max	-1815, 854	-1319, 683
P-value (vs. placebo)[b]	0.0335	--

a A graphical display of individual subject stool weight at baseline versus changes from baseline indicated that treatment effect was dependent on baseline value, and visual impression showed a separation of effect at 740 g baseline stool weight. Therefore, baseline categories were defined as ≤ 740 g (low) and > 740 g (high).
b P-value for baseline mean comparison is from generalized linear model with analysis center as a covariate. P-value for baseline percentage comparison is from CMH test with analysis center as a covariate. The estimates and p values are from the generalized linear model for the change from baseline result, with independent variables: treatment, analysis center, baseline category (value = Low for ≤ 740 g and High for > 740 g in stool weight), and the interaction between treatment and baseline category (if p value > 0.15, the interaction term was not included).
(Table above is taken from Page 36 of the 37554-209 Study Report.)

Study 37554-210 (Phase 3)

Key design features are summarized in the table below.

Table 34. Key Design Features – Study 37554-210

N (total):	▪ 400
Year Conducted	▪ 1998
Key Selection Criteria	▪ HIV adults ▪ Stool weight ≥ 300 g ▪ ≥ 1 abnormal BM (soft or watery) or on anti-diarrheal medication on each of the 14 days prior to the Screening Period
Arms:	▪ Crofelemer 250 mg[#] QID X 6 days (n=102) ▪ Crofelemer 500 mg[#] QID X 6 days (n=100) ▪ Crofelemer 500 mg* QID X 6 days (n=100) ▪ Placebo (n=98)
Primary Endpoint Definition	▪ Change from baseline in daily stool weight during the inpatient period ▪ (Baseline is Day 1; Inpatient Period is Days 2 to 7)

*beads in capsules
[#]tablets

Primary efficacy results are summarized in the table below.

Table 35. Stool Weight: Primary Analysis – ITT Population (Study 37554-210)

Inpatient Period	Crofelemer 250 mg tablets N=102	Crofelemer 500 mg tablets N=100	Crofelemer 500 mg beads N=100	Placebo N=98
Stool weight at baseline (g)				
Mean (SD)	782.1 (506.79)	901.5 (882.50)	705.3 (408.24)	749.4 (475.41)
Median	634.0	641.0	605.5	567.5
Minimum, maximum	300, 2700	193, 7347	300, 3200	317, 3068
P-value (vs. placebo)[a]	0.6886	0.0684	0.6062	-
Categories of stool weight at baseline, n (%)				
Low (≤ 1000 g)	78 (76.5)	79 (79.0)	90 (90.0)	76 (77.6)
High (> 1000 g)	24 (23.5)	21 (21.0)	10 (10.0)	22 (22.4)
P-value (vs. placebo)[a]	0.8390	0.8305	0.0202	-
Change: Baseline to Day 7 (g)				
Mean (SD)	-327.5 (399.78)	-420.1 (894.38)	-309.5 (383.16)	-332.0 (439.97)
Median	-263.0	-259.0	-305.0	-292.5
Minimum, maximum	-1807, 628	-7217, 1498	-2152, 429	-2201, 1149
Least Square Mean (SE)	-440.9 (60.82)	-688.1 (64.14)	-504.8 (85.41)	-472.2 (64.13)
P-value (vs. placebo)[a]	0.7028	0.0107	0.7469	-

a P-value for baseline mean comparison is from generalized linear model with analysis center as a covariate. P-value for baseline percentage comparison is from logistic regression with analysis center as a covariate. The estimates and p values are from the generalized linear model for the change from baseline result, with independent variables: treatment, analysis center, baseline category (low for ≤ 1000 g and high for > 1000 g stool weight), and the interaction between treatment and baseline category (if p value > 0.15, the interaction term is not included).
(Table above is taken from Page 46 of the Study 37554-210 Study Report.)

APPENDIX 4: Interim Analysis Results Used to Select Stage II Dose (Study NP303-101)

Table 36. Stage I, Interim Analysis: Clinical Response, Based on IVRS Data Only and the Data from the 3-day Run-In

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

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

Table above is taken from the Statistics Review. Source is Table 19, Clinical Study Report, NP303-101.)

APPENDIX 5: Clinical Response for Stage I and Stage II (Study NP303-101)

Table 37. Clinical Response Rates for Stage I

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

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

Statistical Reviewer's Note: The p-values and confidence intervals are not adjusted for multiple comparisons and should not be used for making conclusions regarding pairwise comparisons between each treatment group and placebo. Moreover, 'Footnote b' is incorrect – the p-values and confidence intervals are not based on the methods of Posch and Bauer (2005); the p-values are based on asymptotic Pearson chi-square tests and the confidence intervals are Yule confidence intervals.
(Table above is taken from the Statistical Review; source is Table 17, Clinical Study Report for NP303-101.)

Table 38. Clinical Response Rates for Stage II

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

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

Statistical Reviewer's Note: 'Footnote b' is incorrect – the p-values and confidence intervals are not based on the methods of Posch and Bauer (2005); the p-values are based on asymptotic Pearson chi-square tests and the confidence intervals are Yule confidence intervals.
(Table above is taken from the Statistical Review; source is Table 20, Clinical Study Report for NP303-101.)

APPENDIX 6: Distribution of Daily Watery Bowel Movements at Baseline for Stage I and Stage II (NP303-101)

Table 39. Applicant's Analysis Showing Unbalanced Distribution of Daily Watery Bowel Movements at Baseline for Stage I and Stage II

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

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

Table above is taken from the Statistics Review. Source is Table 21 of the NP303-101 Clinical Study Report, page 97

Table 40. Descriptive Statistics for Baseline Daily Watery Bowel Movements by Treatment Group and Stage

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

Table above is taken from the Statistics Review.

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/s/

ANIL K RAJPAL
12/28/2012