

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202292Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	December 14, 2012
<b>From</b>	Andrew E. Mulberg, MD, FAAP, CPI
<b>Subject</b>	Division Deputy Director Summary Review
<b>NDA/BLA #</b> <b>Supplement #</b>	202292
<b>Applicant Name</b>	SALIX PHARMACEUTICALS
<b>Date of Submission</b>	12/5/2011
<b>PDUFA Goal Date</b>	June 5, 2012
<b>Proprietary Name / Established (USAN) Name</b>	Fulyzaq ®/crofelemer
<b>Dosage Forms / Strength</b>	125 mg tablets
<b>Proposed Indication(s)</b>	Control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy
<b>Action/Recommended Action for NME:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Statistical Review	Lisa Kammerman, PhD
Medical Officer Review	Wen-Yi Gao, MD, PhD
Compliance	Khairy Malek, M.D., Ph.D.
Biopharmaceutics	Mark Seggel
DRISK	Carolyn Yancey, MD; Kendra Worthy, MD
Project Management	Kevin Bugin
Botanical Team Review Team Leader	Shaw T. Chen, M.D., Ph.D
Botanical Review Team Reviewer	Jinhui Dou, PhD
Clinical Pharmacology	Kris Estes, RPh, Sue Chih Lee, PhD
Pharmacology Toxicology Review	Sruthi King, PhD, Sushanta Chakder, PhD
CDTL Review	Anil Rajpal, MD

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DDRE= Division of Drug Risk Evaluation

DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

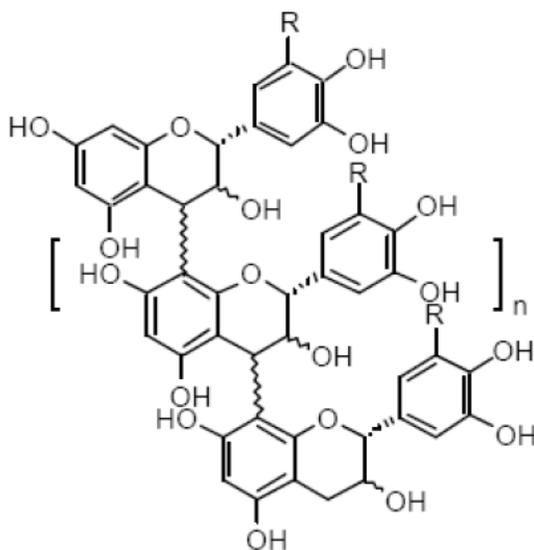
## Signatory Authority Review Template

### 1. Introduction

In this NDA, the applicant proposes to market Fulyzaq (crofelemer) for the following indication in adults:

- 1) control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy

crofelemer is a botanical drug substance (BDS) extracted and partially purified from the red latex of *Croton lechleri* Müll.Arg. in addition, which is comprised of oligomeric proanthocyanidin of multiple chain lengths with an average molecular weight range of 1700 – 2500 Daltons? The monomer units are (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin. The oligomer chains of crofelemer range from 3 to 14 units detected and up to 30 units possible, with an average length of 7-8 units. Its structural formula is:



R = H (procyanidin) and/or R = OH (prodelphinidin)  
n = 1-28; average n = 5

The Applicant presents data from the Study ADVENT (NP-303-01): “Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Two Stage Study to Assess the Efficacy and Safety of crofelemer 125mg, 250 mg, and 500 mg Orally Twice Daily for the Treatment of HIV Associated Diarrhea (ADVENT Trial)”, study (37554-210) and a Phase 2 study (37554-209) (Table 1 below for study description).

Table 1: Description of Study Designs

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

reproduced from Dr Gao's Medical review

In summary, the data in this application establish that crofelemer is effective and is safe for the treatment of patients for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy. The current application decision is approval in light of the the establishment of final details of a suitable clinically relevant bioassay that had previously hindered the initial approval of this application. For further details of this decision, please see below.

## 2. Background

HIV-associated diarrhea often has non-infectious causes including adverse effects of HAART (especially protease inhibitors), HIV enteropathy, HIV-associated malignancies, and pancreatitis. Diarrhea is reported in up to 60% of patients with HIV infection. 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. HIV-associated diarrhea can have a substantial negative impact on quality of life resulting in lack of adherence to HAART regimens as well as the need to change HAART regimens.<sup>1</sup>

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 and are a result of lack of any approved therapeutic regimens for management. Other treatments include non-narcotic, narcotic or anti-

<sup>1</sup> 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.

secretory medications. HAART regimen modification may also be attempted. Non-pharmacologic supportive treatment includes dietary modification such as fiber supplements.

The reader is referred to Dr. Gao's Clinical Review for further discussion of the regulatory history and to Dr. Dou's review for specifics related to the phylogeny of the botanical drug substance comprising crofelemer. Briefly, crofelemer is a botanical drug substance that has been used for generations in regions outside the USA for management of diarrhea. The botanical raw material (BRM) is the latex of *Croton lechleri* Müll.Arg. [Fam. Euphorbiaceae], which is also called dragon's blood (sangre de drago) or tree's blood (sangre de grado). Dragon's blood is an herbal medicine commonly used for the treatment of diarrhea and for wound healing in South America. *C. lechleri*, its latex and partially purified products (such as crofelemer) have been subjects of numerous scientific studies. The review of Dr. Dou should be referenced for additional botanical information.

### **3. CMC/Botanical:**

The CMC issues are more complicated than for a review of a standard NME. The CMC issues concern both botanical drug substance (BDS) and issues related to chemical identification and purification of the product. The issue most relevant for discussion is predicated on the evidence for support of therapeutic consistency in the BDS. There is notable discordance of opinion between the CMC and Botanical reviewers. 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 concluded that issues regarding the identity, strength, purity, and quality of the drug substance and drug product preclude approval. 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.

I do not agree that as per the CMC review that it is necessary to assess the oligomer/polymer distribution in order to detect the source of the proanthocyanidin, and assure the consistency and clinical effectiveness of the drug substance and drug product. This is a botanical product whose constitution by its very nature is more complex and heterogeneous than the purified new molecular entity classically approved by the FDA. I am in total agreement with Dr. Dhou who has noted that botanical new drugs can rarely have CMC specifications as precise as those of pure chemical drugs as new molecular entities (NMEs). Dr. Dhou (Botanicals) has 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. This critical issue relates to the current decision algorithm since it is relevant as will be discussed below.

The Primary Botanical Reviewer concluded that the submitted CMC information supported approval. Botanical products derived from multiple or even single plants are complex mixtures of numerous chemical entities. Even for extensively studied plants, only a small

fraction of the constituents have been isolated and identified. Complete characterization of each individual constituent in botanical drugs, even those derived from a single plant, remains a formidable task. Thus, even in the best case, the chemical composition of a botanical preparation is not completely defined, nor can all active ingredients be necessarily identified. Strength and potency of these vaguely defined products are not easy to determine, adding to the difficulties in CMC controls and clinical pharmacology studies. For example, CMC concerns include adequate characterization by Analytical chemistry including chromatographic, spectroscopic and process control. The BDS perspectives include control of plant raw materials/GACP Processing/cGMP at raw material, support from non-CMC data including the role of a bioassay, dose-response and clinical experiences with multi-batch. The reader is encouraged to review the recent publication of Dr Chen and FDA colleagues on this topic<sup>2</sup>.

Dr Dou concludes that crude plant latex (CPL), commonly known as Dragon's blood has been used commonly as an herbal medicine in Peru and other Central and South American countries for the treatment of diarrhea, cholera, and stomach ulcer, and other GI symptoms. The herbal medicine use of CPL does not suggest any individual component is responsible for the anti-diarrheal activities. The effect of CPL as an antidiarrheal agent in herbal medicine use is consistent with the findings the well-controlled clinical trials. The proanthocyanidin oligomers, the major active components of crofelemer, are similar to the polyphenolics in numerous plant species used as food. Those polyphenolic compounds are considered safe with extensive daily dietary exposure or even beneficial due to their potent antioxidant activities. The previous human uses of CPL dose not reveal serious safety concerns. This is in line with the results of the clinical studies, and animal toxicology studies.

Dr. Dhou notes that the physiological effect of crofelemer (and the related product, SP-303) on CFTR-mediated Cl<sup>-</sup> secretion was evaluated in multiple *in vitro* studies and animal models suggesting that crofelemer had a new mechanism of action for its antidiarrheal effect. Preliminarily clinical studies of crofelemer, including treatment of traveler's diarrhea, were reported to be effective; specifics of the differences in clinical trials are addressed in Dr. Gou's clinical review. Pharmacology studies in the NDA and data from journal publications indicated that the mechanism of crofelemer's antisecretory activities probably involve inhibition of both cyclic cAMP)-stimulated CFTR Cl<sup>-</sup> channel and the CaCC at the luminal membrane of enterocytes, with dose-dependent effects observed in certain *in vitro* bioassays. Dr. Dhou believes that some of the clinical relevant assays, including the proposed bioassay to evaluate (b) (4) may be further developed after approval for quality control purposes, such as to qualifying new CPL sources from new EGRs and cultivated *C. lechleri* trees. From BRT's perspective, the applicant's overall quality control approach, including BRM, manufacturing process, and BDS controls, is adequate and appropriate for approval of the botanical NDA. Dr Dhou did recommend a number of postapproval requirements including making a concerted effort to prevent the over-harvesting of BRM from the wild grown trees in the current EGRs. For example, the applicant should continue to evaluate the applicability of BRM collected from other EGRs, and further analyze the chemical profiles of BRM across different EGRs; investigate other means of qualifying additional EGRs, such as developing and using a medically relevant bioassay or post-approval

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<sup>2</sup> New therapies from old medicines. Shaw T Chen, et al. Nature Biotechnology 2008;26(10): 1077-1083.

bridging clinical studies; and continue efforts to qualify further BRM collected from cultivation sites. The applicant should continue to enforce implementation of CPL quality control, storage, and transportation to prevent contaminations, including contamination from other botanicals.

Importantly, I do not agree that with the recommendation to defer development of a clinically relevant bioassay prior to approval. The obvious lack of critical identification to the satisfaction of Dr. Kowblansky (ONDQA) weighs heavily in my perspective for better characterization of the BDS. 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 concluded that these issues preclude approval. Further specific details are noted in reviews of Dr. Kowblansky and Rajpal. Complete details of the final approved bioassay are discussed by the tertiary review of Dr. Beitz.

It is technically and clinically feasible to develop and validate this assay (b) (4) and control for batch characterization of the BDS in my opinion. Therefore, it is now clear from the Applicant that a bioassay will be developed for better characterization of the BDS. The Applicant is developing such an assay using (b) (4)

As Dr. Rajpal delineates in the CDTL memorandum, there is a proposed timeline for development and validation of a bioassay (b) (4) as discussed above. The Applicant proposed (b) (4) as a bioassay for the characterization of batch-to-batch variation of the drug substance and drug product. The Applicant noted that there is a clear link between the documented cellular mechanism of crofelemer in (b) (4) and the clinical efficacy of the agent in the treatment of secretory diarrhea.

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:

- Use of an assay with a clinically relevant endpoint
- 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
- 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.

The reader is referred to the CMC and Botanical reviews of Dr Dou and Dr Kowblonsky for further details.

To date the provisional data using an (b) (4)

[REDACTED] (b) (4)

The applicant has continued their investigation into developing a bioassay [REDACTED] (b) (4)  
[REDACTED] and that the bioassay seems to be a viable option for supporting approval. Validation data are currently being prepared and evaluated for linearity, repeatability and method precision. The Signatory, Dr. Beitz in her review, will address the final details underlying these conclusions.

#### 4. Nonclinical Pharmacology/Toxicology

From a nonclinical standpoint, this product (125 mg tablet) is approvable for the indications proposed. Dr King notes in her review that there are no significant safety concerns for the proposed dose of crofelemer (125 mg tablet for oral use, twice daily) for the proposed indication, i.e., for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy. The Nonclinical reviewer also recommended labeling changes as detailed in her review, which will not be reiterated here. Changes are recommended to the following section of the label: Sections 8.1 10, 13.1 and 13.2 of the label. The reader is referred to the primary reviews.

#### 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was performed by Kristina Estes, Pharm.D. (May 10, 2012). Dr. Estes did not identify an issue that would preclude approval. [REDACTED] (b) (4)

[REDACTED] (b) (4)

3 [REDACTED] (b) (4)

4 Tradtrantip, L, Namkung, W, Verkman, AS. crofelemercrofelemercrofelemer, an antisecretory antidiarrheal proanthocyanidin oligomer extracted from *Croton lechleri*, targets two distinct intestinal chloride channels. *Mol Pharmacol* 77:69-78, 2010.

5 Crutchley, RD, Miller, J, and Garey, KW. crofelemercrofelemercrofelemer, a novel agent for treatment of secretory diarrhea. *Annal. Pharmacotherapy*. 44:878-84, 2010.

The Biopharmaceutics Reviewer noted that the dissolution profiles will be submitted in a Prior Approval Supplement (PAS) to the NDA [REDACTED] (b) (4). The Biopharmaceutics Review Team is currently determining if this should be a postmarketing commitment

One concern with the dose selection for ADVENT concerns the lack of dose response for crofelemer, but results that demonstrate superiority to placebo. Other studies in different indications including traveler's diarrhea used different endpoints, dosing regimens, treatment duration, and crofelemer formulations. According to Dr. Estes of Clinical Pharmacology, "the dose-response for crofelemer on stool weight and clinical response was determined in the first clinical trial (37554-210) and the first phase of ADVENT, respectively. The doses selected for 37554-210 were 250 mg and 500 mg four times daily and placebo. The doses selected for that ADVENT were 125 mg, 250 mg, and 500 mg twice daily for 4 weeks (primary endpoint) versus placebo, then for an additional 20 weeks in which all placebo patients randomized to one of the three crofelemer doses for the remainder of the time. In study 37554-210, there was no clear dose-response and no consistent response relative to placebo. Multiple dose levels were not included in the Phase 2 study (37554-209), which assessed stool weight following a 4-day treatment with 500 mg crofelemer administered four times daily. It should be noted that only one study (ADVENT) supports the application at the proposed dose." Despite the lack of apparent identification of the lowest effective dose, the intestinal intraluminal concentration of crofelemer exceeds that of the IC<sub>50</sub> to inhibit *in vitro* CFTR activity. This conclusion is supported by Findings from nonclinical primary pharmacology studies demonstrate that crofelemer is a potent selective inhibitor of CFTR and CaCC. The estimated GI lumen concentration of crofelemer following oral administration of the 125 mg BID dose is 178  $\mu$ M, 25-fold and 3.6-fold greater than the IC<sub>50</sub> for CFTR-mediated Cl<sup>-</sup> secretion in T84 cells (IC<sub>50</sub> = 7  $\mu$ M) and Caco-2 cells (IC<sub>50</sub> = 50  $\mu$ M), respectively. These data support the translation of the *in vitro* potency of crofelemer to its clinical efficacy (review by Dr. Estes, Clinical Pharmacology).

The Primary Botanical Reviewer citing the Applicant's Summary of Clinical Pharmacology noted that the estimated gastrointestinal lumen concentration following oral administration of the 125 mg BID dose is 178  $\mu$ M. The IC<sub>50</sub> is 7 $\mu$ M for CFTR-mediated Cl<sup>-</sup> secretion in T84 cells<sup>4</sup> and that the IC<sub>50</sub> is 50  $\mu$ M 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 IC<sub>50</sub> for CFTR-mediated Cl<sup>-</sup> 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 dose, suggesting that the clinical response rates are most likely not affected by minor variations in the quantitative composition of procyanidin oligomers. I concur with these conclusions and believe that the dose is appropriately tested during the clinical trials.

An Approval Action is the final recommendation from the Clinical Pharmacology and Biopharmaceutics disciplines. The Office of Clinical Pharmacology recommends two postmarketing commitments, including an *in vivo* study to evaluate the potential for crofelemer to interact with 3A4 substrates and *in vitro* studies to determine whether crofelemer

is a substrate, inhibitor, or inducer of cytochrome P450 (CYP) enzymes and transporters expressed in the gut.

## 6. Clinical Microbiology

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

## 7. Clinical/Statistical-Efficacy

The reader is referred to Dr. Rajpal’s CDTL memorandum for further review and complete information of efficacy and safety data related to clinical trial and exposure data related to crofelemer. Additional specific issues can be reviewed in the primary Clinical and Statistical reviews of Drs. Gao and Kammerman. Overall, the efficacy data presented in the pivotal trial, Study NP303-101 (ADVENT) (n=376) provides clinical support for approvability. Study NP303-101 was a randomized, double-blind, placebo-controlled (four week) and placebo-free (twenty week), two-stage adaptive study in HIV positive patients on stable anti-retroviral therapy (ART) with a history of diarrhea. The reader is referred to the primary reviews for specific details. 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 2: Reproduced from:** Table 1. Clinical Response Results for 125 mg BID and Placebo BID, Dr. Gao, Clinical review

Parameter/Statistic <sup>a</sup>	Crofelemer 125 mg BID n (%)	Placebo BID n (%)
<b>Combined Analysis (Stage I + Stage II)<sup>b</sup></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: <a href="#">Table 14.2.1.1</a> , Section 14.2; <a href="#">Listing 16.2.6.2</a> , 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.

As noted by Dr. Rajpal, the observed treatment difference of 9.6% is modest but there is an unmet medical need for treatment of HIV associated diarrhea, particularly for patients that do not respond to other anti-diarrheal medications. Furthermore, sensitivity analyses performed by Dr Gao suggest that this effect is magnified in the scenario of patients who have been exposed to multiple antidiarrheal medications. The underlying mechanism of action of

crofelemer in this latter regard remains unexplored. Supportive Phase 2 studies of the mechanism of action and its putative relationship to physiological effect on stool volume and weight are from Studies 37554-209 and 37554-210. The latter two studies were short-term treatment studies in HIV infected patients 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, 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) was noted. 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).

These data support the potential clinical significance of crofelemer in the treatment of diarrhea in this patient population.

Drs Gao, Kammerman and Rajpal recommend a Approval to this application.

## 8. Safety

The reader is referred to the complete safety assessment of Dr. Gao for further information. The current evaluation was based on Study ADVENT, a two-stage study (362 patients) with 4-week placebo-controlled phase and 20-week placebo-free phase. Two supportive placebo-controlled studies [Study 37554-209 (4-day crofelemer treatment in 43 patients) and Study 37554-210 (7-day crofelemer treatment in 302 patients)] were also reviewed. For the primary integrated safety analyses, three pools were used and were defined as follows:

- PC Phase Safety Population in ADVENT: including subjects who received at least one dose of trial drug and had at least one post-baseline safety assessment in the placebo-controlled phase of the ADVENT trial. This information was taken directly from the tables and listings for the ADVENT Clinical Study Report (placebo or crofelemer experience during placebo-controlled phase of ADVENT).
- Long-Term crofelemer Experience Safety Population in ADVENT: including subjects who received at least one dose of crofelemer and had at least one post-baseline safety assessment in the ADVENT trial (crofelemer experience during placebo-controlled and placebo-free phases of ADVENT).
- HIV Integrated Safety Population (Diarrhea in HIV+ Individuals): including subjects who received at least 1 dose of trial drug and had at least 1 post-baseline safety assessment in any of the 3 crofelemer trials for treatment of diarrhea in HIV+ individuals [placebo or crofelemer groups during ADVENT (placebo-controlled and placebo-free phases), 37554-210, and 37554-209].

Important conclusions include the absence of reported drug related deaths (HIV Integrated Safety Population, 696 patients). In addition, Serious Adverse Events (SAEs) were infrequent:

3% (19/696) in crofelemer group, 2% (6/274) in Placebo (HIV integrated safety database). The reported cases of anemia, pneumonia, depression, and suicide attempt were the most frequent SAEs of crofelemer groups, and each reported for 2 subjects (0.3%, 2/696), some of which can be characterized as complications of AIDS. As important is the absence of evidence to suggest an effect on HIV status or ART efficacy (ADVENT study.) In addition, confidence with the safety profile is supported by study of crofelemer in approximately 1,800 subjects in controlled clinical trials in healthy subjects, and patients with diarrhea or viral respiratory diseases:

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

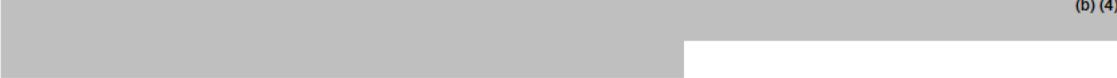
One issue not explicitly discussed by the Clinical reviewer concerns the potential for latex allergy from crofelemer. In additional review by Dr. Gao, there is no allergic report in the integrated population (696 pts) of HIV diarrhea, based on the current submission. According to Dr. Dou of Botanical Products, for crofelemer and this particular *Croton lechleri* latex, there is only one line of cautionary statement on allergy at "Natural Standard": "Avoid with known allergy or hypersensitivity to *sangre de grado* or any of its constituents <http://naturalstandard.com/databases/herbssupplements/all/sangredegrado.asp>. I did see any report about the latex causing allergy to the field collectors; they have been doing this for at least 15 years. There is no special protection needed for the field collectors either. In addition, the popular and extensive human herbal medicine use of the latex did not reveal that allergy is common enough to be a safety concern. The chemical nature of the latex and crofelemer also suggests their safety. Catechins and proanthocyanidins are almost ubiquitous in the plant kingdom, and catechins/polyphenols are not the botanical derived allergens that we worry about. Topically, the latex has been used as "a liquid bandage" for wound healing. Several species of *Euphorbia*, another genus in the same *Euphorbiaceae* family, do produce milky sap, which are toxic and/or causing allergic reactions. The chemicals of concern are terpenoid esters. These stuff are very nasty, some of those herbs are used as very strong laxatives in Chinese medicine. Those *Euphorbia* species are much smaller herbaceous plants, not trees. When the field collectors collect CPL, they will clear the vegetation first to avoid direct contact to other plants. Poison ivy contains urushiol, which is a poisonous oil. Natural rubber is made from the rubber tree latex, which is composed of polyisoprene. Isoprene monomer and oligomers or their derivatives are small enough for causing allergic reactions. These molecules are not water-soluble."

All the crofelemer catechin monomers and proanthocyanidin oligomers are water-soluble and they are the molecules that we have been exposed daily (tea, grape, cocoa). In addition, the (b) (4)

Therefore, I agree with the approval recommendation based on review of the Safety of crofelemer in this population.

## 9. Advisory Committee Meeting

There was not an Advisory meeting held for the discussion of this application. There was a CDER Center briefing held on August 6, 2012 with Janet Woodcock and her senior leadership team with the crofelemer review team. Attendees of this meeting included Janet Woodcock, Robert Temple, Sandra Kweder, Julie Beitz, Victoria Kusiak, Donna Griebel, Andrew Mulberg, Joyce Korvick, Anil Rajpal, Wen-Yi Gao, Sushanta Chakder, Sruthi King; Jinhui Dou. Lisa Kammerman, Mike Welch, Marie Kowblansky, Shaw Chen, Kevin Bugin, Moo Jong Rhee, Kristina Estes, Sue Chih H Lee, Terrance Ocheltree, Christine Moore, Laurie Muldowney, Charles Ganley, Dennis Bashaw, Mary Ann Yancey, and Lee Lemley. The purpose of this briefing was to provide the Center Director with an overview of the application for crofelemer, a botanically derived product indicated for the control and symptomatic relieve of diarrhea in patients with HIV/AIDS on anti-retroviral therapy. There is no approved therapy for treating HIV associated diarrhea. Due to the chemical complexity of this botanical product, ONDQA feels that this NDA has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product. A discussion took place regarding if we could move forward with this application due to its “urgent” need. The concern was that if granted approval, asking the sponsor to submit additional data post-approval, the Sponsor could not submit. crofelemer’s PDUFA date is September 5, 2012. The Center Director Recommendations included the following:

- Dr. Woodcock does not believe that all of the CMC characterization is needed for approvability of this product.
- Sponsor should be asked to submit a potency assay, ie. A bioassay that is clinically relevant that would support the approvability of this compound by demonstrating a relevant relationship to the putative pathobiology of HIV associated diarrhea and impact on the pathophysiological process of chloride secretion. Specific recommendations of the team were to evaluate the feasibility and validation of a (b) (4)  

- Dr. Beitz will make the decision on this NDA application and if there is a dispute, it will be brought to Dr. Woodcock under our appeal process.

## 10. Pediatrics

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 4 weeks because necessary studies are impossible or impracticable.

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:

1975-1            A pediatric study to evaluate pharmacokinetics (PK), efficacy for symptomatic relief of non-infectious diarrhea, and safety with different doses of Fulyzaq (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

## 11. Other Relevant Regulatory Issues

### 11.1 QT Evaluation

*In vitro*, crofelemer produced dose-dependent inhibition of hERG (human ether-a-go-go) K<sup>+</sup> 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 the CDTL Review).

(b) (4) the performance of a thorough QT (TQT) study in humans (submitted under IND 51,818 for crofelemer August 22, 2011) supported by nonclinical and clinical data. A consult was requested from the QT-IRT team on August 25, 2011. (b) (4) The QT-IRT Reviewer noted the following:

(1) crofelemer inhibited hERG currents in a concentration-dependent manner, and the IC<sub>50</sub> is > 100-fold the clinical C<sub>max</sub> exposure;

(2) Following the therapeutic dose of 125 mg BID, the detected crofelemer C<sub>max</sub> 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  $\leq 10$  ms effects.

(b) (4) A letter was sent to the Applicant on October 7, 2011 stating that a TQT assessment should be conducted. 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, which were communicated to the Applicant in a letter dated January 11, 2012. The TQT study was completed, and the Applicant is expected to submit the TQT Study Report to the IND on August 20, 2012. The QT-IRT Team will be consulted to review the TQT Study Report.

## 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 and the summary by Dr. Rajpal. 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

For complete information, see the DMEPA Proprietary Name Review by Manizheh Siahpoushan dated March 9, 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 [REDACTED] (b) (4). Therefore, 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 [REDACTED] (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 [REDACTED] (b) (4). The Applicant submitted a request dated June 27, 2012, that the proposed proprietary name [REDACTED] (b) (4) be withdrawn from review.

Applicant proposed the proprietary name [REDACTED] (b) (4) in a request submitted August 1, 2012. In addition, the Applicant provided for consideration two alternate names (Fulyzaq and [REDACTED] (b) (4)). A final decision regarding name has established Fulyzaq as the tradename for crofelemer.

## 12.1 Office of Prescription Drug Promotion (OPDP) Comments

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

## 12.2 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), conduct a proper work-up to rule out infectious etiologies of diarrhea." (The Applicant had initially proposed, "[REDACTED] (b) (4)")

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).

The DRISK reviewer concludes that a “Risk Evaluation Mitigation Strategy (REMS) is not necessary to ensure that the benefits of crofelemer outweigh the risks in HIV+/AIDS patients with chronic diarrhea, if this product is approved. The proposed labeling adequately addresses the observed safety risks of infectious etiology diarrhea, gastrointestinal events, and abnormal laboratory test results for chemistry parameters observed in the key clinical trials.”

## 13. Decision/Action/Risk Benefit Assessment

### 13.1 Regulatory Action:

The primary reviewers all with exception of ONDQA each recommended an Approval action; Dr. Rajpal has concurred on recommendation for approval for which this Signatory concurs. At the current time based on the current state of bioassay development and the criticality of this assay for making a final decision on action for the NDA, an approval decision is being made as there is establishment of the validated bioassays which are reproducible with crofelemer. Facility performing the assays are ready to test conformance with cGMP (requires an inspection which is currently ongoing and expected by mid-December 2012).

The applicant has continued their investigation into developing appropriate (b) (4)

and that the bioassay seems to be a viable option for supporting approval. Validation data are currently being prepared and evaluated for linearity, repeatability and method precision. The final details underlying these conclusions will be addressed by the Signatory, Dr. Beitz in her review.

### 13.2 Risk Benefit Assessment:

Crofelemer is a complex botanical product and would be the second approved botanical drug. This application bears the complexities of approval of drugs, which balance the complexities of mixtures of chemically active reagents, which prove their clinical benefit by being supported by quality and clinical testing. The nuances of quality control has been fully vetted by the combined teams of ONDQA and Botanicals and discussed with the CDER Director. This is a new paradigm that bears further deliberation as this application bears truth to the complexities of the scenario. In making my Approval decision, I believe that this drug has borne the requirements set forth by Chen and colleagues in a previously published article in 2000<sup>6</sup> pending the successful bioassay development herein described. Description of the botanical, therapeutic consistency and efficacy in clinical trials has been adequately demonstrated with crofelemer; the confirmation of therapeutic consistency requires the completion of the bioassay currently in development. This work is provisionally acceptable to the reviewers and is expected to be completed by end of December 2012 according to the Applicant.

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<sup>6</sup> New Therapies from Old Medicines. Chen ST, Dou J, Robert Temple, Rajiv Agarwal, Kuei-Meng Wu & Susan Walker. Nature 2000;26(10):1077-1083.

**Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:**

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

**Recommendation for other Postmarketing Requirements and Commitments**

The following post marketing commitments below are recommended:

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 1975-4 An *in vitro* study to determine whether crofelemer is an inhibitor of the transporters p-glycoprotein and BCRP.

The timetable you submitted on November 28, 2012, states that you will conduct this study according to the following schedule:

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

- 1975-5 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.

The timetable you submitted on November 28, 2012, states that you will conduct this study according to the following schedule:

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

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

The following postmarketing commitments are being finalized and the tertiary review will reflect all final details:

- 1975-6



(b) (4)

The timetable you submitted on **DATE**, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

1975-7



The timetable you submitted on **DATE**, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

1975-8



The timetable you submitted on **DATE**, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

Submit clinical protocols to your IND 051818 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol,**" "**Postmarketing Commitment Final Report,**" or "**Postmarketing Commitment Correspondence.**"

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANDREW E MULBERG

12/14/2012

Summary review of Division Deputy Director