Long-Term Crofelemer Provides Clinically Relevant Reductions in HIV-Related Diarrhea

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BACKGROUND

- Crofelemer is the only drug that has been specifically studied in and approved for use in managing diarrhea in people living with HIV[1]
- Clinical benefit is derived through reduction of fluid and chloride (Cl-) secretion via potent dual inhibition of cystic fibrosis transmembrane conductance regulator (CFTR) and calcium-activated Cl- channels (CaCC) in the intestinal epithelium[1,2]
- The safety and efficacy of crofelemer in reducing HIV-related diarrhea have been reported in a randomized, double-blind trial (ADVENT)[2]
  - The primary efficacy parameter in ADVENT defined a responder as achieving ≤2 watery stools per week for at least 50% of the 4-week placebo-controlled study period
  - Given that patients in the trial had an average baseline of 20 watery stools per week, a 90% reduction in watery stools per week on average was required to meet the responder definition
  - This criterion fails to characterize the clinically meaningful decrease in watery stools among all patients in the trial. Substantial clinical benefit is likely to occur in this population from a 50% or greater reduction in watery stools
- This supplemental analysis was conducted to provide a more complete understanding of the long-term efficacy of crofelemer in patients with HIV-related diarrhea

OBJECTIVES

The objectives of this analysis were to determine:

- Mean decrease in the number of watery stools per week across the population of the ADVENT trial
- Proportion of ADVENT trial participants who achieved clinically relevant thresholds (50%, 75%, and 100%) for reduction in number of watery stools
- Effect of diarrhea etiology or concomitant protease inhibitor (PI) use on response to crofelemer

METHODS

- The ADVENT trial enrolled HIV+ subjects with noninfectious diarrhea for at least 1 month who were on stable antiretroviral therapy (ART) with CD4+ cell counts ≥100 cells/μL. Details of the methodology have been previously described[2]
- Throughout the study, patients recorded diarrhea symptoms, adherence to study medication and ART, and use of antidiarrheal or prohibited medications through an interactive voice response system (IVRS)
- The current analysis includes patients who received crofelemer 125 mg or placebo twice daily for 4 weeks, after which they had the option of continuing in a 20-week extension phase in which all patients received crofelemer 125 mg BID
  - Daily diary data were analyzed retrospectively from all persons during their treatment with crofelemer 125 mg BID for up to 24 weeks
  - Weekly average reduction in watery stools from baseline (week 0) was determined
  - Data for weeks 5 through 24 for patients who received placebo in the first 4 weeks were shifted to weeks 1 through 20, allowing an assessment of all patients who received crofelemer 125 mg BID at the same time points in active therapy
- Chi-square tests were performed to detect differences in response at each week based on PI use or etiology of diarrhea as determined by the study investigator

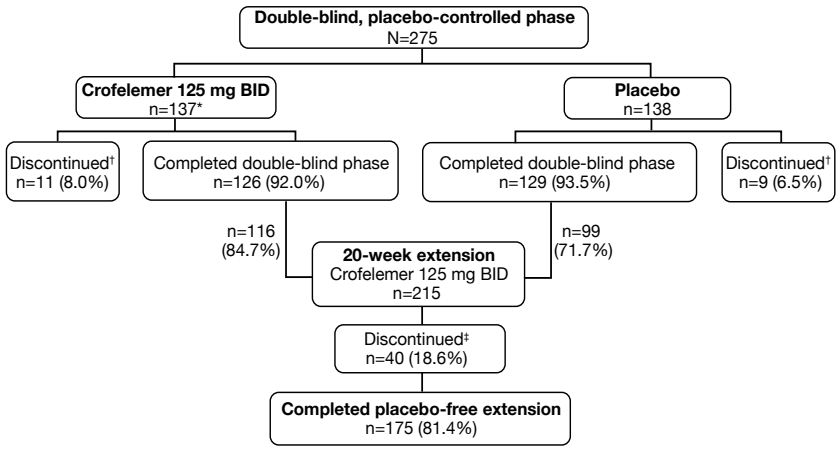
RESULTS

A total of 274 patients were included in the analysis (**Figure 1**). Demographic and baseline characteristics were similar between groups (**Tables 1, 2**). At baseline, patients had experienced diarrhea for an average of 6 years, with an average of 20 watery stools per week. The majority (59%) of patients had previously used at least one antidiarrheal medication.

Table 1. Demographic Characteristics, ITT Population

Characteristics	Placebo (n=138)	Crofelemer 125 mg (n=136)
Mean age, yr (SD)	44.8 (8.4)	45.0 (7.7)
Male, n (%)	116 (84.1)	115 (84.6)
Race, n (%)		
Non-Hispanic white	58 (42.0)	53 (39.0)
Black	53 (38.4)	51 (37.5)
Hispanic	25 (18.1)	31 (22.8)
Other	2 (1.4)	1 (0.7)
Mean time since HIV diagnosis, yr (SD)	12.4 (7.5)	12.4 (6.3)

Figure 1. Patient Disposition



*136 of 137 patients receiving crofelemer were included in intent-to-treat (ITT) population, defined as all randomized patients who received at least 1 dose of randomized study drug.

† Primary reasons for discontinuation included withdrawal of consent, loss to follow-up, adverse event, exacerbation of diarrhea, noncompliance (with IVRS or study drug), and repeated use of antidiarrheal medications or opiates.

‡ Most common reasons for discontinuation were withdrawal of consent, loss to follow-up, and noncompliance with study drug.

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RESULTS (continued)

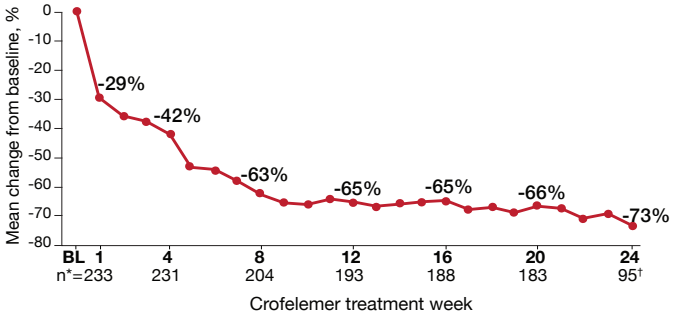
Table 2. Baseline Diarrhea Characteristics, ITT Population

Characteristics	Placebo (n=138)	Crofelemer 125 mg (n=136)
Mean time since diarrhea started, yr (SD)	6.5 (6.5)	5.9 (5.8)
Average number of watery stools per week, mean (SD)	21.3 (14.6)	19.0 (11.6)
Cause of diarrhea, n (%)		
ART	104 (75)	102 (75)
HIV infection of intestine/other	34 (25)	34 (25)
Prior antidiarrheal use, n (%)	83 (60)	79 (58)

Analysis of Reduction in Watery Stools

Analyses of data from all crofelemer-treated patients demonstrated a mean reduction of 65% to 73% in watery stools over 24 weeks of treatment (**Figure 2**).

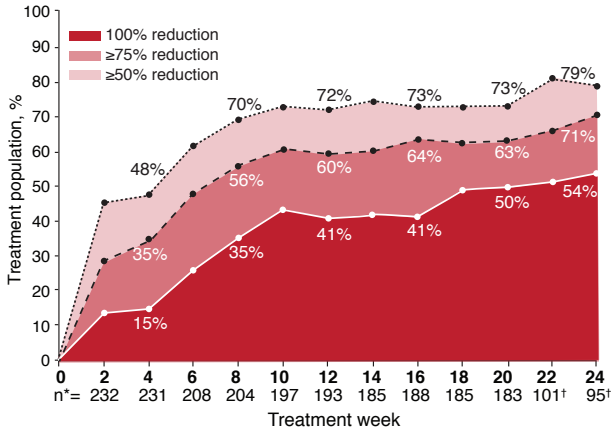
Figure 2. Mean Change in Watery Stools Over Time in Crofelemer-Treated Patients



*Number of patients at each week with evaluable diary data.
†Weeks 21-24 include data only from patients initially randomized to crofelemer.

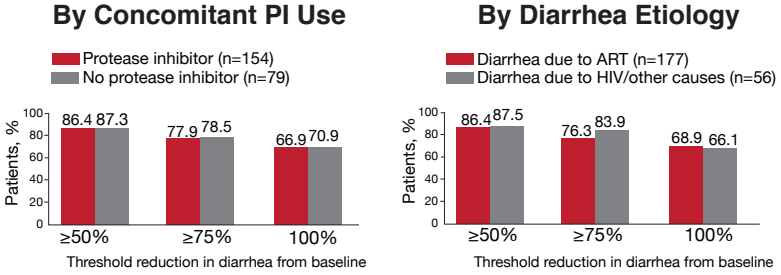
At weeks 4, 12, and 20, a 100% reduction in watery stools occurred in 15%, 41%, and 50% of patients, respectively; a 75% reduction occurred in 35%, 60%, and 63% of patients; and a 50% reduction occurred in 48%, 72%, and 73% of patients (**Figure 3**). Among patients treated with crofelemer who had a decrease in watery stools, 61% had at least a 50% decrease at week 4 and 56% had complete resolution (100% decrease) at week 20.

Figure 3. Proportion of Patients with ≥50%, ≥75%, and 100% Reduction in Number of Watery Stools by Crofelemer Treatment Week



*Number of patients at each week with evaluable diary data.
†Weeks 21-24 include data only from patients initially randomized to crofelemer.

Figure 4. Proportion of Patients Achieving Clinically Relevant Reductions in Watery Stools at Any Study Week*



*No significant differences were observed between groups at any time point.

Crofelemer was well tolerated, with no serious adverse events that were considered to be drug related. The most common adverse events reported were upper respiratory tract infection (5.7%), bronchitis (3.9%), cough (3.5%), flatulence (3.1%), and increased bilirubin (3.1%).

CONCLUSIONS

- Crofelemer achieves much greater reductions in HIV-related diarrhea than was apparent in the original ADVENT trial primary responder analysis[2]
- Crofelemer use resulted in clinically meaningful reductions of diarrhea in most patients, with >75% of patients experiencing ≥50% reduction and over half of patients experiencing complete resolution at week 24
- Results were consistent regardless of concomitant PI therapy or etiology of diarrhea
- Given that an estimated 20% of people living with HIV suffer from diarrhea,[3] in the context of the current worldwide prevalence of HIV (36 million),[4] over 7 million patients worldwide may benefit from the reduction in diarrhea achieved with crofelemer therapy

References

1. Crofelemer [package insert]. San Francisco, CA: Napo Pharmaceuticals, Inc.; 2016. **2.** MacArthur RD, Hawkins TN, Brown SJ, et al. Efficacy and safety of crofelemer for noninfectious diarrhea in HIV-seropositive individuals (ADVENT trial): a randomized, double-blind, placebo-controlled, two-stage study. *HIV Clin Trials*. 2013;14(6):261-273. **3.** Gehrig M, Clay P, Perry R, et al. Actual versus perceived use of pharmacokinetic (primarily absorption) influential OTC agents and ART tolerability in a nationwide matched cohort of HIV patients and their healthcare providers. Poster abstract presented at: ID Week 2016; October 26-30, 2016; New Orleans, LA. Abstract 1514. **4.** World Health Organization. Global Health Observatory data: HIV/AIDS. Available at http://www.who.int/gho/hiv/en/. Accessed May 25, 2017.