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Evalution of Crofelemer in the Treatment of Diarrhea-Predominant Irritable Bowel Syndrome Patients

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Key Words
Irritable bowel syndrome · Diarrhea predominant · Pain- and discomfort-free days · Crofelemer · Chloride secretion

Abstract
Background: Crofelemer improves bowel function in several conditions characterized by states of prominent secretory diarrhea. ***Aim:*** This double-blind, randomized, placebo-controlled trial evaluated the effects of 3 dose levels of crofelemer in patients with diarrhea-predominant irritable bowel syndrome (D-IBS). ***Methods:*** Male and female patients were randomly assigned to receive crofelemer 125, 250 or 500 mg or placebo twice daily for 12 weeks. The primary efficacy measure was a responder for improvement in stool consistency. In addition, abdominal pain- and discomfort-free days, pain and discomfort scores as well as other bowel function parameters (such as stool frequency and consistency, urgency, bloating) were evaluated. ***Results:*** Two hundred and forty-two D-IBS patients were randomized. Crofelemer did not produce significant improvement in stool consistency (primary endpoint), stool frequency, urgency or adequate relief. However, female D-IBS patients showed improvement in the proportion of pain- and discomfort-free days during treatment with 500 mg crofelemer: month 1 (crofelemer vs. placebo: 17.7 vs. 10.2%, p = 0.098); month 2 (23.5 vs. 13.3%, p = 0.076); month 3 (26.1 vs. 10.6%, p = 0.0076). No benefit was seen in male D-IBS patients. Crofelemer was well tolerated. ***Conclusions:*** Crofelelmer did not produce benefit on bowel function; an increase in the number of pain- and discomfort-free days in female D-IBS patients was seen. Further studies with crofelemer are warranted to evaluate it as a potential visceral analgesic.

Introduction

Irritable bowel syndrome (IBS) is a common, chronic gastrointestinal disorder characterized by abdominal pain with abnormal bowel function [1–3]. Alterations in bowel function may present as diarrhea, constipation or an alternation between diarrhea and constipation. These abnormalities in bowel function define IBS subtypes of diarrhea-predominant (D-IBS), constipation-predominant (C-IBS) or alternating (A-IBS) IBS. Patients with IBS have significantly reduced quality of life compared to healthy volunteers, utilize increased health care resources and have increased work absenteeism [4–6]. To date, treatment options for D-IBS patients remain limited.

Crofelemer is a product extracted and purified from the latex of *Croton lechleri*, a plant distributed throughout Western South America [7]. The latex has been used

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as a medicinal product by local indigenous peoples for centuries. Analysis of the latex shows the active compound of interest to be an oligomeric proanthocyanidin of varying chain lengths (averaging 8 units) of approximately 2,300 Da. In several models crofelemer possesses potent antisecretory properties.

Crofelemer inihibits cAMP-mediated chloride ion secretion in Caco-2 and T84 cells [8]. When epithelial cells were pretreated with forskolin, crofelmer inhibited 70% of the short circuit current attributed to chloride ion secretion in Caco-2 cells and 60% in T84 cells [8]. Crofelemer also inhibited 55% of cholera toxin- and heat-labile enterotoxin-stimulated chloride ion secretion in T84 cells [unpubl. results]. Since cAMP-mediated increases in chloride currents in Caco-2 and T84 cells result from activation of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel [8], it has been postulated that crofelemer directly interacts with the CFTR channel.

Based on this antisecretory activity, crofelemer was evaluated in the treatment of diarrhea in acute and chronic settings. Crofelemer produced statistically significant improvement in patients with traveler's diarrhea [9], HIV-associated diarrhea [10] and acute infectious diarrhea [unpubl. results]. The beneficial effects of crofelemer were observed at a dose of 250 mg q.i.d. in adult acute infectious diarrhea, at doses ranging between 125 and 500 mg q.i.d. in traveler's diarrhea and at doses ranging between 250 and 500 mg q.i.d. in HIV diarrhea patients. In the present trial, crofelelmer was evaluated in the treatment of D-IBS.

Methods

Study Design

This was a randomized, double-blind, placebo-controlled study that enrolled men and women with D-IBS from 38 sites in the United States. Approximately 87% of the sites were private practice sites, with the remainder representing university-based practices. After a screening period of up to 14 + 7 days, eligible patients were randomly assigned (1:1:1:1) to receive crofelemer 125, 250 or 500 mg or placebo b.i.d. for 12 weeks. Placebo and the 3 dose levels of crofelemer were administered in identically appearing and tasting tablets. Drug was dispensed at the sites and patients were randomly assigned to treatment according to a computer-generated central randomization scheme with randomization stratified into 4 geographic clusters of centers with a separate randomization scheme within each cluster. Randomization was also stratified to ensure equal gender distributions between treatment groups. Efficacy data were collected using an interactive voice response system (IVRS) [11]. Safety data were collected through spontaneous reports and at scheduled visits throughout the study. The first screening visit occurred on November 3, 2004 and the last study visit was on November 8, 2005.

Study Population

The enrolled patients were at least 18 years of age, male or female, met the Rome II criteria for D-IBS, had an average abdominal pain-discomfort severity score during the 2-week screening period of at least 1 (0 = none; 1 = mild; 2 = moderate; 3 = intense; 4 = severe). Patients also needed to have a mean stool frequency of at least 2 bowel movements per day during screening, a mean consistency score of at least 3 on a 5-point scale (1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery), be fluent in English and provide signed informed consent. Symptoms were required to be recorded through the IVRS, and patients were required to be 75% compliant in completing their daily calls during the screening period. To confirm the absence of organic gastrointestinal disease, a colonoscopy or flexible sigmoidoscopy plus barium enema had to have been performed after the onset of IBS symptoms and within 5 years of the randomization visit for those 50 years of age and older. For those younger than 50 years of age, a flexible sigmoidoscopy needed to be performed within 5 years of randomization. The colon exam was repeated if the nature of symptoms had changed since the previous colon evaluation.

Patients were excluded if they had alcohol or substance abuse within 1 year of the screening visit, had a hospitalization for a major psychiatric condition or suicide attempt within the past 3 years, were pregnant, lactating or had a positive serum β-human chorionic gonadotropin test result during the screening evaluation, had a history or presence of a clinically significant medical disease that might compromise the study or be detrimental to the patient, or had used any investigational treatment within 30 days of the screening visit. Patients were also excluded if they had constipation as defined by less than 3 bowel movements per week for at least 12 weeks in the previous 12 months. Women of child-bearing potential were required to be on a suitable birth control regimen. Other treatments for IBS, laxatives, antidiarrheals, narcotic-containing analgesics and macrolide antibiotics required a 7-day washout period prior to entering the screening period. Antidepressants and antipsychotics were allowed if patients were on a 30-day stable dose prior to screening.

Study Duration

Each patient participated for up to 17 weeks, including a 14-day screening or baseline period, a 7-day randomization window between screening and randomization if required for colon procedures, a 12-week double-blind treatment period and a 14-day posttreatment period. Patients entered data daily on the IVRS from the beginning of the screening period through completion of the follow-up period. Laboratory data and pregnancy tests were performed at each monthly interval, while ECG were done at screening and end of treatment.

All patients receiving at least a single dose of drug were included in the safety population. The population evaluable for efficacy were those patients who received at least a single dose of study medication and who entered at least 1 efficacy evaluation.

Sample Size and Power Considerations

As crofelemer has shown reductions in the time to last unformed stools, watery stool weight and watery stool frequency in

Table 1. Demographics of D-IBS patients randomized

	Placebo (n = 61)	125 mg (n = 62)	250 mg (n = 59)	500 mg (n = 62)
Female, %	75	74	75	74
Mean age, years	47 ± 15.7	49.7 ± 14.0	52.0 ± 12.0	52.1 ± 15.3
Race, %				
White	95	95	92	92
Black	3	3	0	8
Mean baseline pain score	2.37	2.30	2.20	2.23
Mean baseline consistency score	3.88	3.90	3.80	3.81
Mean baseline stool frequency per day	3.97	4.01	3.70	3.38

Pain score: 0 = none; 1 = mild; 2 = moderate; 3 = intense; 4 = severe. Consistency score: 1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery.

previous clinical studies in traveler's and HIV diarrhea patients [9, 10], the present study was powered based on improvement in stool consistency as the primary endpoint. An estimate of the standard deviation of 0.8 was assumed for the weekly stool consistency score using a 5-point consistency scale. A sample size of 55 patients per group would allow detection of a half-point difference between any 2 groups in a two-sided t test at $\alpha = 0.05$ and power at 90%. A sample size of 60 was used to increase the power for detection of changes on secondary endpoints.

It was hypothesized that the antisecretory effects of crofelemer would improve stool consistency in D-IBS patients. Improvement in D-IBS patients is based on improvements in stool consistency, stool frequency, pain scores and pain-free days; even though stool consistency was selected as the primary endpoint in this exploratory phase 2 study, importance was also given to the effects observed on pain, stool frequency and pain-free days. The study, however, was not powered for multiple comparisons, and stool consistency was identified as the primary endpoint, while the other key efficacy parameters were evaluated as exploratory secondary endpoints.

Statistics

The primary analysis scheme was based on the last observation carried forward principle. The primary efficacy endpoint was based on stool consistency. Subjects recorded stool consistency on a daily basis using the following scale: 1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery. The primary endpoint was a stool consistency responder defined as patients with at least a half-point decrease from their baseline stool consistency score. The interval for the primary analysis was a comparison at month 3 to baseline. Stool frequency was collected daily as number of bowel movements passed. Urgency was asked as a daily question: 'Have you had satisfactory control of your bowel urgency today?' This question could be answered 'yes' or 'no'. Patients were asked once every 7 days: 'In the last 7 days, have you had adequate relief of your irritable bowel syndrome symptoms?' The patients could answer 'yes' or 'no' to this question; monthly responders were defined as those with at least 2 weeks per month in which patients replied 'yes'. A whole study responder had at least 50% of the weeks with adequate relief. The pain score (0 = none; 1 = mild; 2 = moderate; 3 = intense; 4 = severe) was collected daily and a pain- and discomfort-free day is equivalent to a score of 0 for a particular day.

Categorical variables were summarized by the number and percentage of subjects in each category. Continuous variables were summarized by total number, mean, standard deviation, minimum, median and maximum values.

Results

Demographics and Disposition

Two hundred and forty-five male and female D-IBS patients were randomized in this study. One patient did not take a single dose of study medication such that the safety population was comprised of 244 patients. Three patients did not answer an efficacy question and 241 patients, therefore, constituted the intent-to-treat (ITT) population evaluable for efficacy. Similar rates of patients completed the study from each treatment group (73–80%). Reasons for withdrawal from the study were also similar across treatment groups. Patient demographics and IBS characteristics are shown in table 1. Most patients (74–75%) were female, Caucasian, with a mean age range of 48–52 years. Groups entered with similar degrees of baseline pain, stool frequency and stool consistency (table 1). Patients entered the study with mean pain scores representing moderate pain (table 1). However, at baseline, stool consistency was basically in the normal range, and stool frequency was somewhat more frequent than expected for normal healthy subject (that is, up to 3 stools/day; table 1).

Summary of Efficacy Analyses

Shown in table 2 is a summary of the efficacy analyses by treatment group for the main efficacy endpoints in-

Table 2. Efficacy results by treatment group at month 3 (last observation carried forward; ITT)

Endpoint	Placebo (n = 60)	125 mg (n = 61)	p	250 mg (n = 59)	p	500 mg (n = 61)	p
Stool consistency							
Responders, %	48	49	0.90	40	0.39	46	0.88
Daily change from baseline	−0.67 ± 0.617	−0.65 ± 0.641	0.81	−0.47 ± 0.639	0.14	−0.48 ± 0.560	0.17
Stool frequency							
Daily change from baseline	−0.98 ± 1.646	−1.05 ± 1.333	0.84	−0.58 ± 0.937	0.89	−0.43 ± 1.186	0.03
Urgency							
Change from baseline, % days with control[1]	30.8 ± 34.8	30.8 ± 31.2	0.99	22.2 ± 32.3	0.41	23.1 ± 32.7	0.46
Adequate relief							
Responders, %	53	57	0.74	40	0.19	54	0.89
Pain score							
Daily change from baseline	−0.73 ± 0.92	−0.82 ± 0.88	0.38	−0.62 ± 0.70	0.94	−0.83 ± 0.85	0.26

Efficacy-evaluable population constitutes patients with at least 1 evaluation. Consistency score: 1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery. Pain score: 0 = none; 1 = mild; 2 = moderate; 3 = intense; 4 = severe.

[1] Urgency: % days with satisfactory control.

Table 3. Pain-free days in ITT and female patients (last observation carried forward)

Population	Placebo (n = 60)	125 mg (n = 61)	p	250 mg (n = 59)	p	500 mg (n = 61)	p
ITT							
Change from baseline at month 1	10.1%	12.0%	0.62	9.4%	0.82	17.3%	0.044
Change from baseline at month 2	15.1%	18.4%	0.54	12.3%	0.57	22.3%	0.15
Change from baseline at month 3	13.1%	19.4%	0.23	13.2%	0.99	24.3%	0.03
Females							
Change from baseline at month 1	10.2%	12.5%	0.68	8.8%	0.72	17.7%	0.098
Change from baseline at month 2	13.3%	19.9%	0.24	12.4%	0.90	23.5%	0.076
Change from baseline at month 3	10.6%	20.5%	0.078	13.3%	0.62	26.1%	0.0076

cluding stool consistency, stool frequency, urgency, adequate relief and pain-discomfort scores. Results are presented at month 3, which was the prospectively determined primary evaluation interval. For the primary endpoint, stool consistency responders, no benefit was seen with any dose of crofelemer compared to placebo. Similar lack of significance was also observed for stool consistency scores and no significant improvement was observed in stool frequency, urgency, adequate relief responders or pain-discomfort scores with any dose of crofelemer compared to placebo.

In the ITT population, significant improvement in pain- and discomfort-free days was observed with 500 mg b.i.d. crofelemer compared to placebo (table 3). Approximately 10% more pain- and discomfort-free days were observed at month 3 compared to placebo (p = 0.03; table 3). Significant improvement was also seen at month 1 and the crofelemer-treated group (500 mg) approached significance at month 2 (table 3).

Analysis of the improvement in pain- and discomfort-free days analyzed by gender showed that the female patient 500 mg b.i.d. cohort was driving the significance in the ITT population. At month 3, there was statistical and clinical improvement in pain- and discomfort-free days in female patients receiving 500 mg crofelemer with an approximate 16% increase in pain- and discomfort-free days (p = 0.0076) over that seen with placebo (table 3). Improvement in pain- and discomfort-free days at 500

Table 4. Most common gastrointestinal adverse events (≥5%) in safety population

	Placebo (n = 61)	125 mg (n = 62)	250 mg (n = 59)	500 mg (n = 62)
Constipation	2	5	3	2
Diarrhea	5	3	3	2
Flatulence	2	2	7	3
Nausea	7	3	3	5
IBS	3	2	0	5
Abdominal pain	2	3	2	5

Table 5. Most common nongastrointestinal adverse events (≥5%) in safety population

	Placebo (n = 61)	125 mg (n = 62)	250 mg (n = 59)	500 mg (n = 62)
Headache	8	5	3	6
Dizziness	2	0	5	0
Pyrexia	3	0	5	0
Influenza	0	5	2	0
Sinusitis	5	5	2	2
URI	0	10	2	3
Pneumonia	0	2	5	0

URI = Upper respiratory infection.

mg b.i.d. in female patients approached statistical significance at month 1 (p = 0.099) and month 2 (p = 0.076) with approximately 7.4 and 10.2% more pain- and discomfort-free days, respectively, in crofelemer-treated female patients compared to that seen with placebo.

Adverse Events

The most frequent adverse events occurring during treatment with crofelemer or placebo are shown in tables 4 and 5. A small number of nongastrointestinal adverse events were observed to occur at a greater frequency with crofelemer treatment than with placebo, and these in general occurred predominantly with the lowest dose level (table 5).

The only gastrointestinal adverse events occurring at a greater rate in the crofelemer arm compared to the placebo arm and occurring at a frequency of at least 5% were: constipation 5% 125 mg crofelemer versus 2% placebo; flatulence 7% 250 mg crofelemer versus 3% placebo; abdominal pain 5% 500 mg crofelemer versus 2% placebo and IBS 5% 500 mg crofelemer versus 3% placebo (table 4). An adverse event of IBS, in general, reflects a worsening of IBS symptoms during the treatment phase of the trial. All other events either occurred at a frequency of less than 5% or at a greater rate on placebo than any dose of crofelemer. No adverse event that lead to discontinuation of patients from the study occurred at a frequency of greater than 3% in any treatment group.

No serious adverse event occurred in more than 1 patient and no serious adverse event was coded as treatment related by study investigators. Evaluation of laboratory values and ECG did not reveal any clinically significant signals during crofelemer treatment.

Discussion

Irreversible ADP-ribosylation of the G protein occurs during exposure of cells to cholera toxin. Life-threatening water and electrolyte loss is a consequence of activation of the CFTR chloride channel with enhanced chloride efflux into the gastrointestinal lumen, followed by water. Toxin-mediated activation of chloride secretion also occurs in other states such as HIV/AIDS-associated diarrhea and traveler's diarrhea and crofelemer produces improvement in stool frequency and consistency in these disorders [9, 10].

The lack of effect of crofelemer on stool consistency or stool frequency in the present study may reveal important information about the nature of the diarrhea observed in IBS patients. The present results may implicate the lack of involvement of CFTR-mediated chloride secretion in the genesis of diarrhea in D-IBS patients; at least in the 'general' D-IBS patient population, although efficacy may be seen in selected D-IBS subgroups. Unlike conditions such as cholera, infectious or traveler's diarrhea, the diarrhea associated with IBS does not represent a continuous secretory state as patients with IBS are generally not awakened with the need to defecate during the night. Additionally, diarrhea in IBS seldom leads to dehydration, orthostatis or electrolyte abnormalities. This is not to be confused with the fact that D-IBS patients suffer great impairments in quality of life due to the presence of pain and diarrhea with urgency. In fact, D-IBS patients score abnormally low on both generic and disease-specific quality of life instruments [4–6]. Alternatively, the lack of effect of crofelemer on stool consistency may also reflect that, at baseline, patients' stool consistency scores were fundamentally in the normal range and that since

crofelemer appears not to produce constipation there was a floor effect on stool consistency scores and significant changes were therefore not observed. Evaluation of crofelemer in patients with looser baseline stool consistency scores is warranted.

By contrast to its effects on bowel function, crofelemer produced improvement in pain- and discomfort-free days. Although laxatives and antidiarrheals can be used to modulate bowel function in C-IBS and D-IBS patients, respectively, they do not improve the visceral pain associated with IBS. Previously, a preliminary report [12] showed benefit with crofelmer on other parameters by excluding outlier data. However, these analyses were exploratory and post hoc.

An in vivo absorption and tissue distribution study in rats has shown that crofelemer has the unique attribute that it is minimally absorbed (approx. 1% of the administered dose), and this attribute also translates to man [unpubl. data]. Crofelemer's effects are, therefore, mediated through activity within the gastrointestinal lumen. Thus, if crofelemer was to be confirmed to improve pain- and discomfort-free days, without having a significant potential for systemic toxicity, this would be of potential advantage in the therapy of IBS.

In this study, the dose of 250 mg b.i.d. did not produce any improvement in pain- and discomfort-free days in D-IBS patients, or on bowel function parameters. The exact reason for this finding is unknown, although many factors, including patient adherence, differing pain thresholds and differences in release characteristics of the crofelemer formulation, could have contributed to the lack of benefit from this dose of crofelemer. For instance, in a separate D-IBS trial conducted in female D-IBS patients, a different formulation of crofelemer, providing twice the dissolution of the formulation used in this study was evaluated. Consistent with the results obtained with the 250 mg b.i.d. dose in this study, a lower dose of 125 mg b.i.d. with the new formulation was found to be non-efficacious in ameliorating pain- and discomfort-free days or other bowel function parameters in female D-IBS patients in that study.

With the Rome III reclassification scheme for IBS subtypes [13], a cohort of IBS patients is now recognized that does not have prominent bowel function disturbance. Given the beneficial effects on pain- and discomfort-free days, the potential use of an agent, such as crofelemer, that does not induce diarrhea or constipation in other IBS subtypes, may represent a desirable treatment option as it has the potential to be used in all IBS subtypes and not negatively impact bowel function.

Identification of the mechanism by which an agent that is a partial antagonist of the luminal CFTR chloride channel resides in the gastrointestinal lumen and improves visceral pain may shed important light on the mechanism of pain generation in IBS. While there are a few reports evaluating the etiology of abdominal pain and discomfort in IBS, there is evidence that clinically meaningful relief in IBS patients is influenced significantly by the number of abdominal pain- and discomfort-free days. This is supported by the observation that lubiprostone, an agent that stimulates chloride secretion into the gastrointestinal lumen, reduces visceral pain in C-IBS patients [14].

Thus, both mechanistic studies detailing the pathway by which inhibition of lumen CFTR and other chloride-secreting channels can lead to visceral analgesia as well as further exploration of crofelemer in other IBS patient subtypes should be performed.

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Appendix

Investigator List (Sites 101–142)

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