Randomized, Double-blind, Placebo-controlled, Phase 2 Trial of Ondansetron 12 mg Bimodal Release Tablets for Diarrhea Predominant Irritable Bowel Syndrome (IBS-D)

Poster
Su1188

Terry Plasse[1*], Gary Barton[2], Evelyne Davidson[3], Louis Velez[4], Danielle Abramson[1], Gilead Raday[1], Reza Fathi[1], Ira Kalfus[1]
[1]RedHill Biopharma, Tel Aviv, Israel; [2]Arkansas Gastroenterology, PA, North Little Rock, AR; [3]New Phase Research & Development, Knoxville, TN; [4]Applied Research Center of Arkansas, Little Rock, AR. *Corresponding author

Abstract:

Objective: Diarrhea predominant irritable bowel syndrome (IBS-D) responds to a 5-HT3 antagonist, alosetron, but that drug has problematic toxicity. Exploratory studies of ondansetron, a 5-HT3 antagonist used for treatment of nausea and vomiting, suggest efficacy in IBS-D without major toxicities noted with alosetron. This study assessed efficacy and safety of once daily 12 mg bimodal release (3 mg immediate/9 mg extended release) ondansetron (BRO: RHB-102, BEKINDA®) in IBS-D.

Methods: Male and female patients (pts) with IBS-D per Rome III criteria, Bristol stool scale (BSS) score ≥6 at least 2 days weekly, and average daily worst pain intensity ≥3 on a 10-point Likert scale were randomized 60:40 to BRO or placebo (PBO). Pts with other causes for abdominal pain and loose stools were excluded, as were pts with baseline C-reactive protein (CRP)>2X ULN. Pts were treated for 8 weeks. Weekly stool consistency response, the primary endpoint, was defined as ≥50% reduction in days per week with ≥1 BM with BSS score 6 or 7 compared with baseline, and abdominal pain unchanged or improved. Weekly pain response was defined as decrease in weekly average worst abdominal pain in the past 24 hours score ≥30% compared with baseline and number of days per week with at least one stool with consistency of type 6 or 7 the same as or decreased from baseline. Weekly composite endpoint was achievement of both stool consistency and pain objectives the same week. Overall response required achievement of the respective response for ≥4 of the planned 8 weeks of treatment. Modified intent to treat (mITT) analysis was conducted on all patients who received any study medication.

Results: Treatment groups were well matched; median age was 40 years; median duration of IBS-D was 4.4 years; 30% of pts were male; average daily stool consistency per Bristol stool scale (BSS) was 5.8; median worst abdominal pain was 5; median CRP 2.09 mg/L (ULN=5.0 mg/L).

Overall response parameter	BRO (N=75), %	PBO (N=51), %	Difference, %	P=
Stool consistency*	56.0	35.3	20.7	0.036
CRP≤median	52.6	48.0	4.6	0.919
CRP>median	59.5	23.1	36.4	0.009
Pain	50.7	39.2	11.5	0.278
Composite	40.0	25.5	14.5	0.135

*Primary endpoint

56.0% of BRO vs 35.3% of PBO pts had a stool consistency response (p=0.036). Pain and composite endpoint responses were more common in BRO than PBO pts. Treatment effect was primarily in pts with baseline CRP>median. Effect of baseline CRP on both pain and composite endpoints was similar to effect on stool consistency. Treatment effect on stool consistency was similar in males and females. BRO was well tolerated, with a higher rate of constipation in the BRO-treated group (13.3% vs. 3.9%), which resolved rapidly with withholding treatment, and a similar overall rate of adverse events across treatment groups. No serious adverse events were reported.

Conclusions: In this multicenter double-blind study, ondansetron 12 mg bimodal release tablets were effective and safe in the treatment of both men and women with IBS-D. Baseline CRP was predictive of treatment effect.

Note: final data, corrected from original submission

Background:

Diarrhea predominant irritable bowel syndrome (IBS-D) is a common, chronic illness characterized by recurrent abdominal pain and loose or watery stools. Current diagnosis, per Rome III criteria, is based on signs and symptoms. There is no pathologic finding which characterizes IBS, and its etiology is unknown.
Several medications are approved for treatment of IBS-D.

- One 5-HT3 antagonist, alosetron (Lotronex®), is approved for treatment of IBS-D, but only for women who have severe IBS-D
- Rarely, patients taking alosetron may develop serious gastrointestinal adverse reactions, including ischemic colitis and complications of constipation

Ondansetron, another 5-HT3 antagonist, has been used for treatment of chemotherapy- and radiotherapy-induced nausea and vomiting for over 25 years.

- Several small pilot studies have demonstrated efficacy of ondansetron in treatment of IBS-D.
- While constipation is a known side effect of ondansetron, ischemic colitis and other complications of constipation have not been reported.

RHB-102 (BEKINDA®) is an investigational, proprietary once daily **b**imodal **r**elease **o**ndansetron (BRO) formulation containing:
3 mg immediate release ondansetron and
9 mg extended release ondansetron for delivery over 24 hours

Methodology:

Randomized, parallel group, placebo controlled trial in patients with IBS-D per Rome III criteria and who had average worst daily pain intensity ≥3.0 for each of two baseline weeks.
Key entry criteria included :

- Loose or watery stools (Bristol Stool Scale 6 or 7) ≥2 days/week
- Exclusion by history, physical and laboratory assessments of other conditions which could lead to symptomatology similar to IBS-D
- No major laboratory abnormality or other conditions which might preclude assessment of safety or efficacy
- Patients with QTc interval prolongation >450 msec on screening ECG, or who were taking medication known to cause QT prolongation were excluded.

After baseline data were collected and a 2-week observation period during which stool consistency and frequency and overall symptomatology data were collected, qualifying patients were stratified by gender and randomized 60:40 to RHB-102 (BRO) 12 mg versus placebo. one tablet daily for 8 weeks.
If a patient developed constipation, he or she was to reduce dosing to once every other day.
Patients completed diaries for stool consistency (per the Bristol Stool Scale), abdominal pain and abdominal distress.
Primary endpoint: stool consistency response: defined per 2012 FDA guidance on IBS-D: Per week, patient experienced ≥50% reduction in the number of days with at least one stool that has a consistency of Type 6 or 7 on the Bristol stool scale compared with baseline.
In addition, patient could not have had an increase in average abdominal pain >10% over baseline during that week.
Overall stool consistency responder: patient was a weekly responder ≥50% of the planned weeks of treatment.
Secondary endpoints:

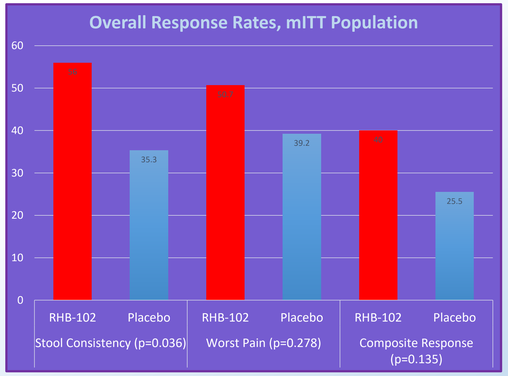
- Pain responder: per FDA guidance, a patient who experienced a decrease in the weekly average of worst abdominal pain in the past 24 hours score ≥30% compared with baseline and no increase in the number of days per week with Type 6 or 7 stool consistency
  Overall pain responder: patient who was a weekly pain responder for ≥50% of planned treatment weeks
- Composite weekly responder: patient who met both the stool consistency and pain response definitions for a given week
  Composite study responder: patient who met criteria for weekly composite response ≥50% of planned treatment weeks
- Additional efficacy assessments and occurrence and severity of adverse events were also recorded and compared between treatment groups.

Laboratory abnormalities were considered AEs if they developed on study or increased ≥1 grade per NCI CTCAE v 3.04 criteria, regardless of investigator significance assessment.
Modified intent to treat (mITT) population: all patients randomized and who received at least one dose of study medication, analysed by treatment to which randomized
Safety population: all patients who received at least one dose of study medication, analysed by treatment received

- In this study, the mITT and safety populations were identical.

Patient Demographics	RHB-102 (N=75)	Placebo (N=51)	Total (N=126)
Age (years), median	44.0	38.0	40.0
Range	19-74	18-68	18-74
Sex n (%)			
Male	22 (29.3)	16 (31.4)	38 (30.2)
Female	53 (70.7)	35 (68.6)	88 (69.8)
Race n (%)			
Asian	11 (14.7)	6 (11.8)	17 (13.5)
Black or African American	5 (6.7)	3 (5.9)	8 (6.3)
White	58 (77.3)	42 (82.4)	100 (79.4)
Other	1 (1.3)	0 (0.0)	1 (0.8)
Hispanic ethnicity n (%)	9 (12.0)	4 (7.8)	13 (10.3)
Weight (kg), median	74.5	79.0	75.4
Range	44.6-150.0	41.8-137.9	41.8-150.0

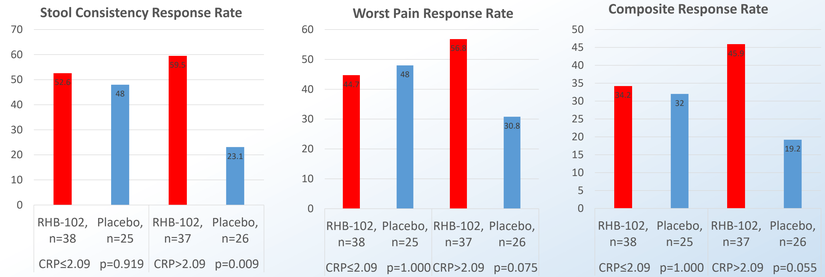
History and Baseline Characteristics	RHB-102	Placebo	Total
Characteristic	(N=75)	(N=51)	(N=126)
Time since first symptoms of IBS (years), median	5.1	3.5	4.4
Range	1-42	1-43	1-43
Patients with at least one moderate IBS symptom	70 (93.3)	47 (92.2)	117 (92.9)
Patients with at least one severe IBS symptom	37 (49.3)	23 (45.1)	60 (47.6)
Diary-Based Baseline Values: 2-week observation period			
Worst Abdominal Pain, median	4.9	5.0	5.0
Range	0-8	0-8	0-8
Average daily frequency of defecation, median	2.2	1.9	2.0
Range	1-6	1-4	1-6
Average Daily Stool Consistency (as measured on Bristol Stool Scale)			
Median	5.8	5.9	5.8
Range	3-7	4-7	3-7
Baseline C-reactive Protein, mg/L, median	2.07	2.25	2.09
Range	0.14-26.02	0.18-9.63	0.14-26.02
N (%) ≤5.0 (upper limit of normal)	63 (84)	39 (76)	102 (81)
N (%) >5.0 to ≤10.0	11 (15)	12 (24)	23 (18)
N (%) >10.0	1 (1)	0	1 (1)



Effect of Gender on Response

Parameter	Response rate, %			
Gender	RHB-102	Placebo	Difference	p=
n, male/female:	22/53	16/35		
Stool consistency overall response rate				
Male	50.0	31.3	18.8	0.41
Female	58.5	37.1	21.3	0.081
Worst pain overall response rate				
Male	54.5	25	29.5	0.137
Female	49.1	45.7	3.3	0.929
Composite overall response rate				
Male	36.4	18.8	17.6	0.296
Female	41.5	28.6	12.9	0.313

Relationship between Baseline CRP and Response



Baseline CRP and Response: Logistic Regression Model

	Treatment effect[a]			Baseline CRP effect[b]		
	CRP	Odds Ratio	p-value	Treatment	Odds ratio	p-value
Stool consistency	≤median	1.204	0.719	RHB-102	1.32	0.552
	>median	4.889	0.006	Placebo	0.325	0.067
Worst pain	≤median	0.877	0.799	RHB-102	1.621	0.299
	>median	2.952	0.045	Placebo	0.482	0.211
Composite	≤median	1.105	0.856	RHB-102	1.635	0.301
	>median	3.57	0.033	Placebo	0.506	0.3

[a]Reference: placebo; [b]Reference: CRP≤median

While statistically significant, this unexpected relationship between baseline CRP and treatment effect was based on a small number of patients. The finding should be considered tentative pending completion of further studies.

Adverse Event/Safety Parameters	RHB-102 (N=75) n (%)	Placebo (N=51) n (%)	Total (N=126) n (%)
Patients with any treatment-emergent adverse event (TEAE)	68 (90.7)	47 (92.2)	115 (91.3)
Patients with worst TEAE=mild	40 (53.3)	35 (68.6)	75 (59.5)
Patients with worst TEAE=moderate	16 (21.3)	9 (17.6)	25 (19.8)
Patients with worst TEAE=severe	12 (16.0)	3 (5.9)	15 (11.9)
Patients withdrawn from treatment due to adverse events	2 (2.7)	0 (0.0)	2 (1.6)
SOC/adverse events occurring in ≥10% of patients in either treatment group			
Gastrointestinal disorders	20 (26.7)	5 (9.8)	25 (19.8)
Constipation	10 (13.3)	2 (3.9)	12 (9.5)
Infections and infestations	12 (16.0)	10 (19.6)	22 (17.5)
Investigations	59 (78.7)	42 (82.4)	101 (80.2)
Blood glucose increased	17 (22.7)	9 (17.6)	26 (20.6)
Blood sodium decreased	4 (5.3)	7 (13.7)	11 (8.7)
Protein urine present	27 (36.0)	17 (33.3)	44 (34.9)
White blood cells urine positive	23 (30.7)	17 (33.3)	40 (31.7)
Nervous system disorders	9 (12.0)	8 (15.7)	17 (13.5)
Headache	7 (9.3)	6 (11.8)	13 (10.3)

Moderate to severe GI AEs were experienced by 10.6% of RHB-102 patients but no placebo patients. Constipation was moderate to severe in 5.3% of RHB patients but no placebo patients.
Constipation was controlled in most cases by decreasing dosing frequency. One patient discontinued treatment due to constipation and one due to painful defecation associated with constipation. In both cases, symptoms resolved without sequelae after discontinuation of study medication. No other patients discontinued treatment due to AEs.

Discussion

- RHB-102 (bimodal release ondansetron) given daily for 8 weeks significantly improved stool consistency in patients with IBS-D.
  - Similar effects were noted in males and females.
  - Trends towards improvement in pain and composite responses were also noted.
  - While direct comparisons to other treatment modalities are not possible due to differences in evaluation procedures, results with RHB-102 indicate a robust treatment effect, given the small sample size and design of the study.
- Baseline C-reactive protein was a strong predictive factor for treatment effect for each of the 3 parameters studied, as demonstrated in prospectively planned analyses:
  - The major effect was a decrease in response rates in the placebo group in patients with baseline CRP>median, with a smaller increase in response rates in RHB-102 recipients.
  - These effects were confirmed in post hoc logistic regression analyses.
- Constipation was the major side effect noted:
  - Constipation was more common in RHB-102 patients than in placebo recipients but was controlled by reduced dosing frequency.
  - The incidence of constipation with RHB-102 was similar to that reported for eluxadoline or alosetron 0.5 mg bid but lower than that reported for alosetron dose 1 mg bid.
- No serious adverse events occurred.

Conclusions

- RHB-102, a bimodal release, once daily ondansetron formulation, significantly improved stool consistency, demonstrating a robust treatment effect in patients with IBS-D.
  - In addition, there was a trend towards improvement of pain and composite endpoint.
  - The drug was active in both males and females.
- A prospective analysis by baseline CRP demonstrated markedly higher treatment effect in patients with CRP above median.
- RHB-102 was well tolerated.
- Bimodal release ondansetron at a dose of 12 mg daily may be a useful and well tolerated treatment for IBS-D.
- Further study of RHB-102 with additional assessment of the role of baseline CRP is warranted.