Gastrointestinal Adverse Events Observed With Berotralstat (BCX7353) Treatment for Hereditary Angioedema Are Primarily Mild, Self-limited, and Diminish With Time on Treatment

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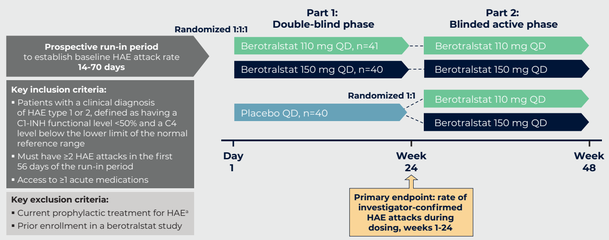
INTRODUCTION

- Hereditary angioedema (HAE) is a rare disease caused by uncontrolled plasma kallikrein activity and bradykinin dysregulation, leading to unpredictable, potentially life-threatening recurrent swelling attacks most commonly affecting the extremities, face, abdomen, and larynx.[1-4]
- Berotralstat (BCX7353) is an oral, once-daily, highly selective inhibitor of plasma kallikrein in development for prophylaxis of HAE attacks.
- Berotralstat significantly reduced the frequency of HAE attacks compared with placebo in the APeX-2 study.[5]
- Berotralstat was safe and generally well tolerated at both the 110-mg and 150-mg doses with mild gastrointestinal (GI) events reported as the most common treatment-emergent adverse events (TEAEs) associated with berotralstat.[6]
- This analysis further characterizes the GI TEAEs observed with berotralstat treatment over 24 weeks in part 1 of the APeX-2 study.

METHODS

- Patients were randomized 1:1:1 to berotralstat 110 mg, berotralstat 150 mg, or placebo once daily for 24 weeks in part 1, after which all patients were continued on active drug blinded to dose (**Figure 1**).

Figure 1. APeX-2 Study Design



C1-INH, C1 esterase inhibitor; C4, complement 4; HAE, hereditary angioedema; QD, once daily. [a]Prophylactic treatments constituting exclusion included using C1-INH within 14 days before screening visit, using androgens or tranexamic acid within 28 days before screening visit, or initiating use of any of these drugs for prophylaxis during the trial.

- TEAEs were defined as AEs that occurred on or after the first dose of study drug.
- AEs were assessed by the investigator as grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life-threatening), according to the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table.[7]
- Investigators assessed relatedness of AEs to study drug.
- GI abdominal TEAEs were prospectively defined as preferred terms within Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 hierarchy under the High-Level Group Terms of 1) GI signs and symptoms and 2) GI motility and defecation conditions.
- Incidence of TEAEs occurring in part 1 of APeX-2 was analyzed overall and by month (4-week intervals) of onset.

RESULTS

- 121 patients were randomized to treatment (**Table 1**).

Table 1. Summary of Baseline Demographics and Disease Characteristics

Patient characteristic, n (%)[a]	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=40)	Total (N=121)
Age, mean (SD), y	40 (18)	40 (14)	45 (14)	42 (15)
Female	30 (73)	23 (58)	27 (68)	80 (66)
Race				
White	38 (93)	38 (95)	37 (93)	113 (93)
Region				
North America	32 (78)	27 (68)	28 (70)	87 (72)
Europe	9 (22)	13 (33)	12 (30)	34 (28)
Any prior prophylactic treatment for HAE	32 (78)	30 (75)	29 (73)	91 (75)
Any prior androgen use	19 (46)	21 (53)	25 (63)	65 (54)
Any prior C1-INH use[b]	16 (39)	21 (53)	16 (40)	53 (44)
≥2 HAE attacks/month[c]	28 (68)	30 (75)	27 (68)	85 (70)

C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; SD, standard deviation. [a]Unless otherwise indicated. [b]C1-INH includes plasma-derived and recombinant C1-INH and fresh frozen plasma. [c]Baseline investigator-confirmed attack rate is defined as (total number of investigator-confirmed HAE attacks experienced in the period between screening and first date/time of study drug) × 28/(date of first dose - date of screening +1).

- 120 patients received ≥1 dose of study drug.
- The incidence of TEAEs was similar in all 3 groups over the 24-week period, occurring in 82.9%, 85.0%, and 76.9% of patients receiving 110 mg, 150 mg, and placebo, respectively.
- The system organ class (SOC) with the most TEAEs reported was the GI disorders SOC. GI abdominal TEAEs are presented in **Table 2**.

Table 2. Overall Summary of GI Abdominal TEAEs

Safety outcomes, n (%)	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=39)
Any GI abdominal TEAE	17 (41.5)	20 (50.0)	14 (35.9)
Any drug-related TEAE	14 (34.1)	14 (35.0)	11 (28.2)
Any TESAE	0	0	0
Any drug-related TESAE	0	0	0
Any grade 3 or 4 TEAE	2 (4.9)	0	0
Any drug-related grade 3 or 4 TEAE[a]	2 (4.9)	0	0
Any TEAE leading to interruption of study drug	0	0	0
Any TEAE leading to discontinuation of study drug[b]	1 (2.4)	0	0
Any TEAE that required use of concomitant medication	5 (12.2)	4 (10.0)	3 (7.7)

GI, gastrointestinal; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event. [a]Berotralstat 110 mg: abdominal pain (n=2). [b]Berotralstat 110 mg: dyspepsia, nausea, vomiting (1 patient experienced all 3 events).

- GI abdominal TEAEs were predominantly mild (grade 1); 2 patients in the berotralstat 110-mg group experienced grade 3 abdominal pain. Neither discontinued berotralstat.
- Only 1 patient (110 mg) discontinued study drug due to a GI abdominal TEAE; the patient had a history of GERD and discontinued due to moderate dyspepsia, nausea, and vomiting.
- Most GI abdominal TEAEs (87.8%, 90.0%, and 92.3% in the 110-mg, 150-mg, and placebo groups, respectively) resolved without the use of concomitant medication.
- Abdominal pain, when all locations are combined (eg, abdominal pain, abdominal pain upper), was the most commonly reported GI abdominal TEAE in patients treated with berotralstat.
- The most common individual GI abdominal TEAEs were nausea, vomiting, dyspepsia, and diarrhea (**Table 3**).
- GI abdominal TEAEs were common regardless of treatment group. Nausea and abdominal distention occurred more frequently on placebo than on berotralstat and several other events occurred at similar frequencies in all groups.

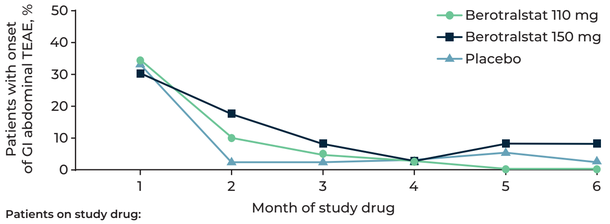
Table 3. Most Commonly Reported GI Abdominal TEAEs

Safety outcomes, n (%)	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=39)
Any GI abdominal TEAE[a]	17 (41.5)	20 (50.0)	14 (35.9)
Nausea	6 (14.6)	6 (15.0)	7 (17.9)
Vomiting	4 (9.8)	6 (15.0)	1 (2.6)
Dyspepsia	4 (9.8)	3 (7.5)	3 (7.7)
Diarrhea	4 (9.8)	5 (12.5)	0
Abdominal pain	2 (4.9)	4 (10.0)	2 (5.1)
Abdominal discomfort	1 (2.4)	3 (7.5)	3 (7.7)
Flatulence	2 (4.9)	3 (7.5)	1 (2.6)
Gastroesophageal reflux disease	4 (9.8)	2 (5.0)	0
Abdominal distention	1 (2.4)	1 (2.5)	2 (5.1)
Abdominal pain upper	1 (2.4)	2 (5.0)	1 (2.6)
Constipation	1 (2.4)	0	1 (2.6)
Abdominal tenderness	1 (2.4)	0	0
Change of bowel habit	1 (2.4)	0	0
Eructation	1 (2.4)	0	0
Frequent bowel movements	0	1 (2.5)	0

GI, gastrointestinal; TEAE, treatment-emergent adverse event. [a]GI abdominal AEs are defined as any AE with a preferred term within the MedDRA 19.1 hierarchy under the High-Level Group Terms of 1) GI signs and symptoms or 2) GI motility and defecation conditions.

- The most common GI abdominal TEAEs associated with berotralstat treatment were abdominal pain, vomiting, and diarrhea. These events were generally mild and well tolerated.
- GI abdominal TEAEs occurred primarily in the first month: 34.1%, 30.0%, and 33.3% of 110-mg, 150-mg, and placebo patients, respectively (**Figure 2**).

Figure 2. Incidence of New-Onset GI Abdominal TEAEs by Month



Patients on study drug:						
Berotralstat 110 mg	41	41	41	41	40	38
Berotralstat 150 mg	40	40	37	37	37	37
Placebo	39	39	38	37	36	34

GI, gastrointestinal; TEAE, treatment-emergent adverse event.

- In the second month, GI abdominal TEAEs were more common in patients receiving 110 mg (9.8%, n=4) and 150 mg (17.5%, n=7) compared with those receiving placebo (2.6%, n=1).
- By the third month, incidence of GI abdominal TEAEs was less than 10% in all groups (110 mg: 4.9%, n=2; 150 mg: 8.1%, n=3; and placebo: 2.6%, n=1).

CONCLUSIONS

1. Berotralstat was safe and generally well tolerated at both the 110-mg and 150-mg doses.
2. GI abdominal TEAEs were common in all treatment groups, including placebo.
3. The incidence of GI abdominal TEAEs declined quickly after the first month in all treatment groups.
4. GI abdominal TEAEs were predominantly mild, self-limited, and approximately 90% resolved without the use of concomitant medication.
5. Only 1 patient discontinued due to a GI abdominal TEAE.

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