Oral Prophylaxis With Berotralstat (BCX7353) Reduces Use of Standard-of-Care On-Demand Medication in Patients With Hereditary Angioedema: APeX-2 Study Results

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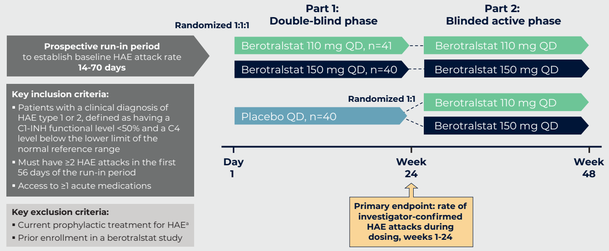
INTRODUCTION

- Hereditary angioedema (HAE) is a rare disease characterized by unpredictable, potentially life-threatening recurrent swelling attacks most commonly affecting the extremities, face, abdomen, and larynx.[1,2]
- Angioedema attacks are mediated by dysregulation in the bradykinin-forming pathway.[3]
- Uncontrolled plasma kallikrein activity leads to overproduction of bradykinin, which results in vasodilation, vascular leakage, and consequent swelling.[3,4]
- 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 and was found to be safe and generally well tolerated in the APeX-2 study.[5,6]
- Here we present an analysis of the use of standard-of-care on-demand medication during part 1 of the APeX-2 study (24 weeks).

METHODS

- APeX-2 is a phase 3, double-blind, placebo-controlled, parallel-group study of berotralstat 110 mg or 150 mg in patients with HAE (**Figure 1**).
- Patients with HAE with ≥2 attacks in up to 56 days were randomized 1:1:1 to receive berotralstat 110 mg or 150 mg or placebo for 24 weeks.
- At week 24, patients were continued on the same dose of berotralstat or, for placebo patients, randomized 1:1 to either 110 mg or 150 mg of berotralstat.

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.

- Patients were to treat any HAE attacks occurring on study in accordance with their usual acute treatment plan.
- The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during dosing in the 24-week treatment period (part 1).
- Rate of investigator-confirmed HAE attacks treated with on-demand medication (ie, icatibant, plasma-derived C1 esterase inhibitor [C1-INH], ecallantide, or recombinant C1-INH) over the 24-week treatment period (part 1) was an exploratory endpoint. The rate of on-demand medication use was an ad hoc analysis.
- Statistical analyses were based on a negative binomial regression model.

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.
- In the primary efficacy endpoint analysis, both berotralstat groups had lower rates of investigator-confirmed attacks over 24 weeks compared with the placebo group (**Table 2**).

Table 2. Rate of Investigator-Confirmed HAE Attacks per 28 Days During the 24-Week Double-blind Part 1 (Primary Efficacy Endpoint)

Primary efficacy endpoint[a]	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=39)[b]
Rate of investigator-confirmed attacks per month during entire dosing period	1.65	1.31	2.35
Attack rate ratio (relative to placebo)	0.70	0.56	—
Rate reduction (%) vs placebo (95% CI)	30.0 (4.6, 48.7)	44.2 (23.0, 59.5)	—
P value	0.024	<0.001	—

CI, confidence interval; HAE, hereditary angioedema. [a]Statistical analysis is based on a negative binomial regression model. The number of investigator-confirmed attacks is included as the dependent variable, the treatment is included as a fixed effect, baseline investigator-confirmed attack rate is included as a covariate, and the logarithm of duration on treatment is included as an offset variable. [b]40 patients are in the analysis population; 1 patient did not dose and therefore has no attack data for part 1.

- The rate of investigator-confirmed attacks treated with on-demand medication was also significantly lower in both berotralstat dose groups compared with placebo (110-mg group, 36.9% reduction, nominal *P*=0.015; 150-mg group, 49.2% reduction, nominal *P*<0.001; **Table 3**).

Table 3. Rate of Investigator-Confirmed HAE Attacks Treated With On-Demand Medication[a]

	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=39)[b]
Rate of investigator-confirmed attacks treated with on-demand medication	1.29	1.04	2.05
Attack rate ratio (relative to placebo)	0.63	0.51	—
Rate reduction (%) vs placebo (95% CI)	36.9 (8.6, 56.4)	49.2 (25.5, 65.4)	—
Nominal *P* value	0.015	<0.001	—

CI, confidence interval; HAE, hereditary angioedema. [a]Statistical analysis is based on a negative binomial regression model. The number of investigator-confirmed attacks is included as the dependent variable, the treatment is included as a fixed effect, baseline investigator-confirmed attack rate is included as a covariate, and the logarithm of duration on treatment is included as an offset variable. [b]40 patients are in the analysis population; 1 patient did not dose and therefore has no attack data for part 1.

- The rates of on-demand medication use were significantly reduced in both the 110-mg (46.3%, nominal *P*=0.002) and the 150-mg (53.6%, nominal *P*<0.001) dose groups compared with placebo (**Table 4**).

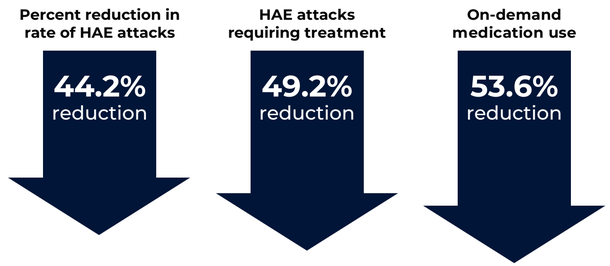
Table 4. Rates of On-Demand Medication Use per 28 Days for Investigator-Confirmed Attacks[a]

	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=39)[b]
Rate of on-demand medication use per month (doses/month)[c]	1.50	1.29	2.79
Rate ratio (relative to placebo)	0.54	0.46	—
Rate reduction (%) vs placebo (95% CI)	46.3 (19.7, 64.1)	53.6 (29.8, 69.3)	—
Nominal *P* value	0.002	<0.001	—

CI, confidence interval. [a]Statistical analysis is based on a negative binomial regression model. The number of rescue medication doses is included as the dependent variable, the treatment is included as a fixed effect, baseline investigator-confirmed attack rate is included as a covariate, and the logarithm of duration on treatment is included as an offset variable. [b]40 patients are in the analysis population; 1 patient did not dose and therefore has no on-demand medication data for part 1. [c]Based on ad hoc analysis.

- The reduction in rate of on-demand medication use equates to approximately 1.3 and 1.5 fewer doses of on-demand medication per month for the 110-mg and 150-mg dose groups compared with placebo, respectively.
- The percent reduction in on-demand medication use was greater than would be expected solely by the reduction in attack rate for both doses (**Figure 2**).

Figure 2. Rate Reductions in HAE Attacks, Treated Attacks, and On-Demand Medication Use: Berotralstat 150 mg vs Placebo[a]



HAE, hereditary angioedema. [a]See **Tables 2**, **3**, and **4** for details on statistical analysis for percent reduction in rate of HAE attacks, HAE attacks requiring treatment, and on-demand medication use, respectively.

- The most frequent adverse drug reactions were mild-to-moderate gastrointestinal events that were brief in duration and self-limited (**Table 5**).

Table 5. Adverse Drug Reactions Occurring in >10% of Patients and Occurring More Frequently (Difference of ≥5%) in Either Berotralstat Group Than the Placebo Group

Adverse drug reaction, n (%)[a]	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=39)
Abdominal pain[b]	4 (9.8)	9 (22.5)	4 (10.3)
Vomiting	4 (9.8)	6 (15.0)	1 (2.6)
Diarrhea[c]	4 (9.8)	6 (15.0)	0
Back pain	1 (2.4)	4 (10.0)	1 (2.6)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term. [a]Adverse drug reactions are either the MedDRA-coded PTs (MedDRA version 19.1) of vomiting or back pain or are medical concepts of diarrhea and abdominal pain that contain multiple AE PTs. [b]Abdominal pain contains PTs of abdominal pain, abdominal discomfort, abdominal pain upper, and abdominal tenderness. [c]Diarrhea contains PTs of diarrhea and frequent bowel movements.

CONCLUSIONS

1. Patients receiving berotralstat had fewer attacks, treated fewer attacks, and used less on-demand medication compared with placebo.
2. The percent reduction in the rate of on-demand medication use was greater than the reduction in both treated and overall attack rates, suggesting reduced attack severity for patients on berotralstat.
3. Rate reductions in treated attacks and on-demand medication use indicate benefit beyond reduction in the rate of attacks.
4. The most frequent adverse drug reactions were mild-to-moderate GI events that were brief in duration and self-limited.

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