Patterns of Treatment and Retreatment of Acute Attacks of Hereditary Angioedema With Standard-of-Care On-Demand Medication: Results From the APeX-2 Study

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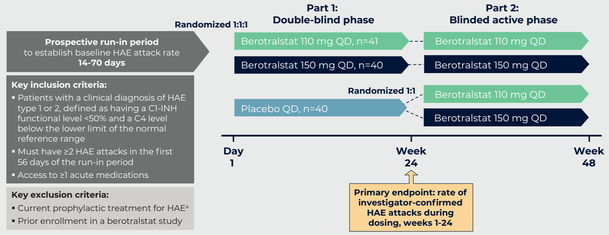
INTRODUCTION

- 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 patterns of care data from part 1 of the large, prospective APeX-2 study and an exploratory analysis evaluating treatment and retreatment of HAE attacks with standard-of-care on-demand medications.

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.
- Eligible patients were randomized 1:1:1 to berotralstat 110 mg or 150 mg, or placebo once daily for 24 weeks (part 1). 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**).

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.

- All patients were required to have access to a targeted on-demand medication during the study.
- Patients were to treat any HAE attacks occurring on study in accordance with their usual acute treatment plan.
- Patients maintained daily diaries of HAE attacks, which included symptoms of the attack and details on initial and subsequent treatments used.
- The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during dosing in the 24-week treatment period (part 1).
- The use of HAE attack medications over 24 weeks was an exploratory endpoint.
- Statistical analyses were based on a negative binomial regression model.
- Only targeted medications for the treatment of HAE attacks (ie, icatibant, plasma-derived C1 esterase inhibitor [C1-INH], ecallantide, or recombinant C1-INH) were included in this analysis.

RESULTS

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

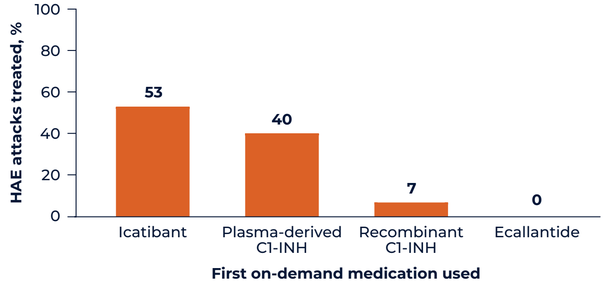
Table 1. Summary of Baseline Demographics and Disease Characteristics

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 on-demand medications most commonly used first to treat investigator-confirmed HAE attacks across all groups in part 1 were icatibant and plasma-derived C1-INH therapies (used to treat 53% and 40% of attacks, respectively; **Figure 2**).

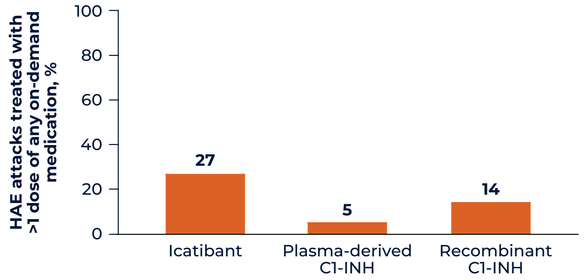
Figure 2. Percentage of Investigator-Confirmed Treated HAE Attacks by First On-Demand Medication Used, All Treatment Groups Combined



C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema. Ecallantide was not used as the first medication for HAE attacks in part 1 and is not discussed further in this poster. Percentages reflect the first targeted on-demand medication given for an investigator-confirmed HAE attack.

- Across all treatment groups, retreatment (ie, treatment with >1 dose) was most common when icatibant was the first on-demand treatment used to treat an HAE attack. Across all groups, 27% of HAE attacks treated with icatibant were later treated with ≥1 additional dose of on-demand medication vs 5% for plasma-derived C1-INH and 14% for recombinant C1-INH (**Figure 3**).

Figure 3. Percentage of Investigator-Confirmed HAE Attacks Treated With >1 Dose of On-Demand Medication, by First On-Demand Medication Used, All Treatment Groups Combined[a]



C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema. [a]Percentages reflect investigator-confirmed HAE attacks that were treated with a targeted medication.

- In the primary efficacy endpoint analysis, the 110-mg and 150-mg berotralstat doses reduced investigator-confirmed HAE attacks by 30% (*P*=0.024) and 44% (*P*<0.001), respectively, compared with placebo.
- The rate of on-demand medication use per 28 days was significantly lower in both berotralstat dose groups compared with placebo (110-mg group, 46% reduction, nominal *P*=0.002; 150-mg group, 54% reduction, nominal *P*<0.001; **Table 2**).

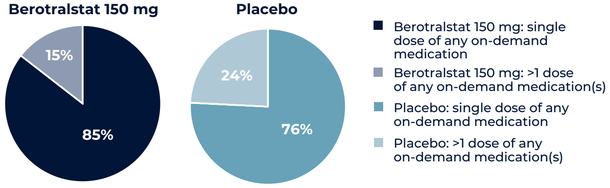
Table 2. Rates of On-Demand Medication Use per 28 Days for Investigator-Confirmed Attacks, Part 1, by Treatment Group[a]

	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 percentage reduction in on-demand medication use (46% and 54%) was therefore greater than the reduction in overall attack rates (30% and 44%) for berotralstat 110 mg and 150 mg.
- A higher percentage of HAE attacks in the 150-mg dose group (85%) were treated with a single dose of on-demand HAE attack medication than in the placebo group (76%; **Figure 4**).

Figure 4. Percentage of Investigator-Confirmed HAE Attacks Treated or Retreated With Any On-Demand Medication[a]



HAE, hereditary angioedema. [a]Percentages reflect investigator-confirmed HAE attacks that were treated with a targeted medication.

- Icatibant was used more often as the first treatment for HAE attacks in the placebo group (67% of attacks) than in the berotralstat 150-mg group (42% of attacks); however, when evaluating only HAE attacks in the placebo and berotralstat 150-mg dose groups that were first treated with icatibant, the percentage of HAE attacks treated with a single dose was higher in the 150-mg group (74%) than in the placebo group (66%).

CONCLUSIONS

1. The percent reduction in on-demand medication use with berotralstat 150 mg (54% relative to placebo) was greater than the reduction in attack rate (44% relative to placebo).
2. The percentage of HAE attacks retreated with on-demand medication was lower for the 150-mg group than the placebo group.
3. Taken together, these suggest reduced attack severity with berotralstat.

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