Long-term Effectiveness of Berotralstat (BCX7353) for the Prophylaxis of Hereditary Angioedema (HAE) Attacks: Interim Results From the APeX-S Study

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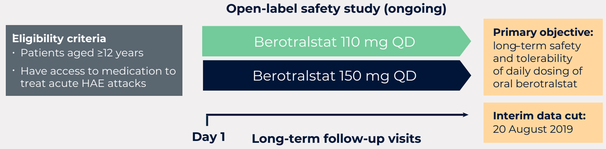
INTRODUCTION

- 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 (NCT03485911).[5,6]
- Here we present an interim analysis of the long-term effectiveness of both 110-mg and 150-mg doses of daily oral berotralstat from the ongoing open-label APeX-S safety study (NCT03472040).

METHODS

- APeX-S is an ongoing open-label study of berotralstat 110 mg or 150 mg in patients with HAE type 1 or 2 (**Figure 1**).
- Patients were centrally allocated to receive open-label berotralstat 110 mg or 150 mg.

Figure 1. APeX-S Study Design



HAE, hereditary angioedema; QD, once daily.

- The primary objective was to evaluate the long-term safety and tolerability of daily dosing of oral berotralstat in patients with HAE.
- Patients were required to have access to appropriate medication for the treatment of acute HAE attacks.
- The secondary objective was to assess the effectiveness (ie, HAE attack frequency, severity, and disease activity over time) and quality of life (QoL).
- Data on HAE attacks were reported by patients daily using a diary.
  - Patient-recorded attacks were reviewed and confirmed or rejected programmatically according to predefined rules before inclusion in effectiveness analyses.
  - Programmatically defined attacks were termed “adjusted attacks.”
- Quality of life was assessed using the disease-specific questionnaire, Angioedema Quality of Life (AE-QoL), in countries where validated translations were available.

RESULTS

BASELINE CHARACTERISTICS

- At the time of this interim analysis, 100 patients received berotralstat 110 mg and 127 received 150 mg (**Table 1**).
- Patients were enrolled at 49 sites in 22 countries across the United States, Europe, Israel, Asia, Australia, New Zealand, and South Africa.

Table 1. Summary of Baseline Demographics and Disease Characteristics

Patient characteristics, n (%)[a]	Berotralstat 110 mg (n=100)	Berotralstat 150 mg (n=127)	Total (N=227)
Age, mean (SD), y	37.6 (14.0)	42.5 (13.4)	40.3 (13.9)
Age			
12-17 y	5 (5)	5 (4)	10 (4)
18-64 y	93 (93)	119 (94)	212 (93)
≥65 y	2 (2)	3 (2)	5 (2)
Female	62 (62)	77 (61)	139 (61)
Weight, mean (SD), kg	75.7 (19.1)	78.7 (18.9)	77.4 (19.0)
Race			
Asian	12 (12)	10 (8)	22 (10)
White	82 (82)	110 (87)	192 (85)
Other	6 (6)	7 (6)	13 (6)
Any prior prophylactic treatment for HAE	81 (81)	102 (80)	183 (81)
Any prior androgen use	61 (61)	81 (64)	142 (63)
Any prior C1-INH use[b]	22 (22)	32 (25)	54 (24)

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.

- Treatment compliance with study drug was high: mean (±SD), 95% (±9.4) over 48 weeks (**Table 2**).

Table 2. Patient Exposure

Parameter	Berotralstat 110 mg (n=100)	Berotralstat 150 mg (n=127)	Total (N=227)
Duration of exposure, mean (±SD), days[a]	253 (±128.6)	307 (±143.3)	283 (±139.3)

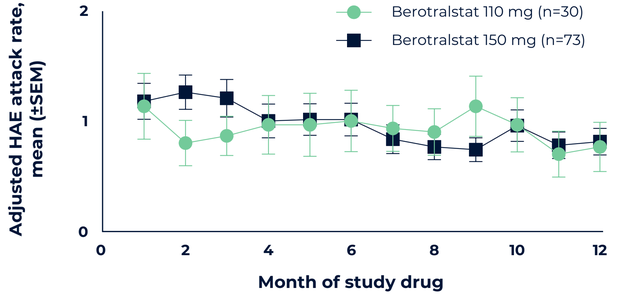
SD, standard deviation. [a]Data for duration of exposure are for the overall safety population.

- Overall, 45% of patients (n=103, 30 on 110 mg and 73 on 150 mg) had completed their 48-week visit at the time of the data cut.

LONG-TERM EFFECTIVENESS AT 48 WEEKS

- Mean and median HAE attack rates were consistently low over 48 weeks of treatment with oral berotralstat.
- After 1 month of treatment, patients in the berotralstat 110-mg (n=30) and 150-mg (n=73) dose groups who received berotralstat through week 48 had mean (±SD) HAE attack rates of 1.13 (±1.634) and 1.18 (±1.398) attacks per month, respectively.
- The mean (±SD) rate of HAE attacks was relatively steady during months 2 to 6 and then generally improved from months 6 to 12 from 1.00 (±1.531) and 1.01 (±1.264) attacks per month in month 6 to 0.77 (±1.223) and 0.81 (±1.031) attacks per month in month 12 for the 110-mg and 150-mg groups, respectively (**Figure 2**).

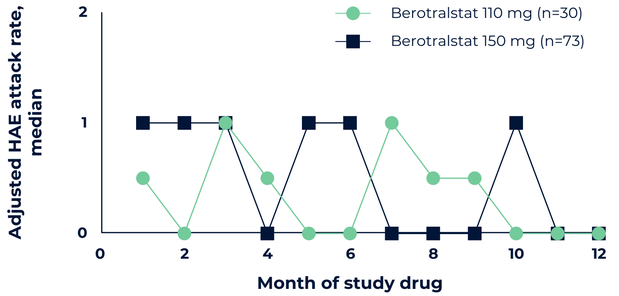
Figure 2. Mean Adjusted HAE Attack Rate by Month, Patients Completing 48 Weeks of Dosing



HAE, hereditary angioedema; SEM, standard error of the mean.

- Median HAE attack rates followed a similar trend.
- Patients in the berotralstat 110-mg and 150-mg dose groups who received berotralstat through 48 weeks had median (range) attack rates of 0.5 (0.00, 7.00) and 1.0 (0.00, 7.00) attacks per month at month 1, and 0.0 (0.00, 5.00) and 1.0 (0.00, 6.00) attacks per month at month 6, respectively.
- The median (range) HAE attack rate was 0.0 (0.00, 4.00) per month at month 12 for both dose groups (**Figure 3**).

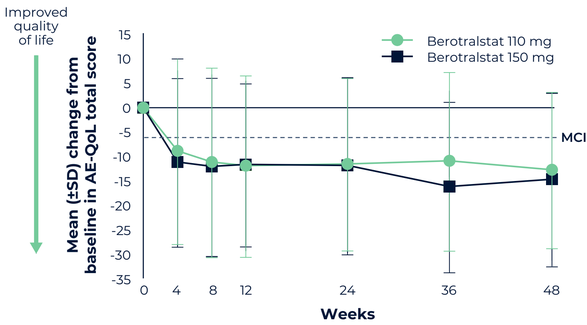
Figure 3. Median Adjusted HAE Attack Rate by Month, Patients Completing 48 Weeks of Dosing



HAE, hereditary angioedema.

- Clinically meaningful improvements in mean AE-QoL total scores were observed at week 48 for both dose groups.
- Improvements in mean change from baseline AE-QoL total score exceeding the minimum clinically important difference (MCID = 6) were observed by week 4 for both dose groups (**Figure 4**).
- At week 48, the mean (±SD) change from baseline in AE-QoL total score for the berotralstat 150-mg treatment group was -14.7 (±17.75) points.

Figure 4. Mean Change From Baseline AE-QoL Total Score by Month



Berotralstat 110 mg, n	84	81	73	70	65	53	23
Berotralstat 150 mg, n	118	114	113	107	100	89	73

AE-QoL, Angioedema Quality of Life; MCID, minimum clinically important difference; SD, standard deviation.

CONCLUSIONS

1. Patients on oral berotralstat had low attack rates, which were maintained or improved over 48 weeks.
2. Clinically meaningful improvements in mean AE-QoL total score were observed and persisted through week 48.
3. In this interim analysis, patients with HAE had low attack rates thus reducing disease burden and improving patient quality of life.

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