Growth-Related Berotralstat Dose Adjustment in Children with Hereditary Angioedema: 48-Week Dosing Experience from APeX-P

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INTRODUCTION

- Hereditary angioedema (HAE) is a rare, autosomal dominant disorder that typically presents in early childhood and has a substantial disease burden that affects daily life.[1,2]
- HAE is treated with on-demand medications for acute attacks and with long-term prophylaxis (LTP) to prevent future attacks.[3]
- Previously approved prophylactic treatments for children aged <12 years require parenteral administration, which can be challenging in pediatric patients.[4]
- Berotralstat, an oral, small-molecule plasma kallikrein inhibitor, is approved in the USA, Japan, and the EU for LTP of HAE attacks in children aged ≥2 years.[5–7]
  - In patients aged 2 to <12 years, berotralstat dosing is based on body weight.[5–7]
- This analysis evaluated the effect of berotralstat dose adjustment during the first 48 weeks of APeX-P on safety outcomes.

METHODS

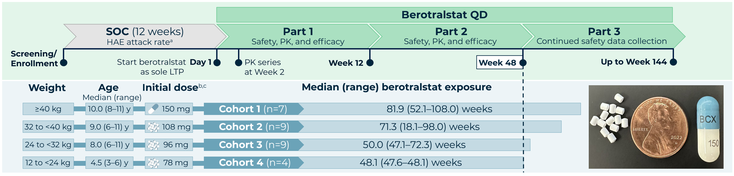
- APeX-P (NCT05453968; EU CTN 2024-511257-22-00) is an ongoing, single-arm, open-label, Phase 3 trial evaluating berotralstat in patients with HAE due to C1-inhibitor deficiency aged 2 to <12 years and weighing ≥12 kg (**Figure 1**).[8]
- Before berotralstat initiation, patients received standard of care (SOC) for 12 weeks.
  - During the SOC period, all patients had access to on-demand treatment; some patients also received LTP.
- Patients were assigned to one of four cohorts based on body weight on Day 1 of berotralstat treatment, with dose escalation permitted after Week 12 as patients' weight increased.
  - Patients received berotralstat pellets or capsules depending on their body weight: pellets in those weighing <40 kg and capsules in those weighing ≥40 kg.

Figure 1. APeX-P Study Design



Inclusion
- HAE-C1INH diagnosis
- Age 2 to <12 years
- Body weight ≥12 kg
- Patient would benefit from oral LTP in the opinion of the investigator

Exclusion
- Any clinically significant medical condition or medical history that would interfere with patient safety or study participation



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HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema due to C1-inhibitor deficiency; LTP, long-term prophylaxis; n, number of patients; PK, pharmacokinetics; QD, once daily; SOC, standard of care; y, years.
[a]Severity of HAE attacks as reported in patient diaries. [b]Dosing cohorts refer only to patients' starting dose and could be adjusted in response to weight change, safety events, or PK results. [c]Cohort 1 received berotralstat capsules, and Cohorts 2, 3, and 4 received pellets.

RESULTS

Baseline Characteristics and Dose Adjustment

- Overall, 29 patients were enrolled in the APeX-P trial, of whom six (20.7%) received a weight-based dose adjustment during the first 48 weeks of berotralstat treatment.
  - At screening, these six patients (2 male, 4 female) had a mean (standard deviation [SD]) age of 9.2 (1.5) years (**Table 1**).
  - At baseline, they had a median (range) body weight of 33.2 (28.0–37.8) kg (**Table 1**).

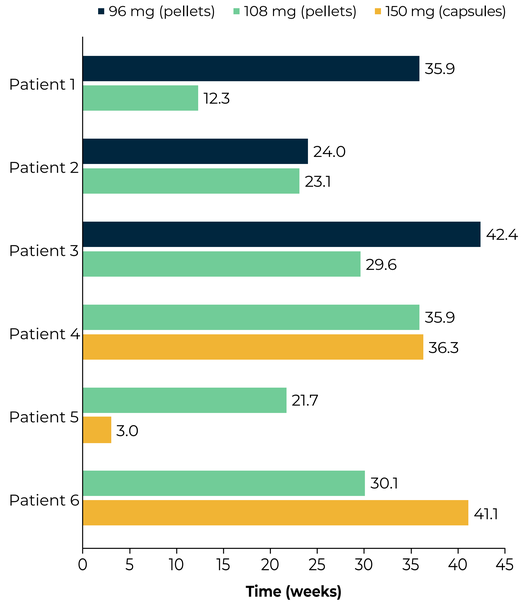
Table 1. Patient Demographics and Baseline Characteristics

	Total (N=6)
Age at screening, years	
Mean (SD)	9.2 (1.5)
Median (range)	8.5 (8–11)
Body weight at baseline,[a] kg	
Mean (SD)	33.3 (4.4)
Median (range)	33.2 (28.0–37.8)
Age at symptom onset, years	
Mean (SD)	3.0 (3.5)
Median (range)	1.0 (0.3–8.0)
Age at diagnosis, years	
Mean (SD)	1.6 (0.8)
Median (range)	1.5 (0.8–3.0)
Race,[b] n (%)	
White	4 (66.7)
Unknown	2 (33.3)
Sex at birth, n (%)	
Female	4 (66.7)
Male	2 (33.3)

N, total number of patients; n, number of patients in specified category; SD, standard deviation.
[a]Defined as the latest non-missing result prior to administration of the first dose of berotralstat.
[b]Some sites in France reported "Unknown" for race due to local regulations.

- Children remained at their initial dose level for 21.7–42.4 weeks before any weight-based dose adjustment occurred (**Figure 2**).
  - After dose adjustment, three patients continued to receive the pellet formulation and three switched from pellets to capsules.

Figure 2. Time Spent on Each Berotralstat Dose by Patient



Patients underwent one weight-based dose increase.
Durations of exposure before and after dose change are factors of when the participant met weight-based thresholds for dose modification and timing of the data cut for this presentation.

Safety

- Before dose adjustment, treatment-emergent adverse events (TEAEs) and drug-related TEAEs were reported by four (66.7%) and one (16.7%) of the six patients, respectively (**Table 2**).
  - The number of patients reporting TEAEs or drug-related TEAEs was unchanged following dose adjustment.
- No drug-related serious TEAEs or discontinuations related to adverse events were reported.

Table 2. Treatment-Emergent Adverse Events

	Before dose adjustment (N=6)	After dose adjustment (N=6)
TEAEs, n (%)	4 (66.7)	4 (66.7)
TEAEs occurring in ≥1 patient,[a] n (%)		
Nasopharyngitis	2 (33.3)	1 (16.7)
Headache	2 (33.3)	0 (0.0)
Cough	2 (33.3)	0 (0.0)
Drug-related TEAEs, n (%)	1 (16.7)	1 (16.7)
Serious TEAEs, n (%)	0 (0.0)	0 (0.0)
Drug-related serious TEAEs, n (%)	0 (0.0)	0 (0.0)
Any TEAE leading to drug discontinuation, n (%)	0 (0.0)	0 (0.0)

Safety data include data from the entire duration of berotralstat exposure as of the data cutoff on March 24, 2025.
N, total number of patients in the sample; n, number of patients reporting an event; TEAE, treatment-emergent adverse event.
[a]Three most commonly occurring TEAEs by preferred term reported.

CONCLUSIONS

1. The ongoing APeX-P study is the largest trial to date of LTP in patients with HAE aged 2 to <12 years.
2. In this analysis, berotralstat dose adjustment was well tolerated and did not lead to an increase in the number of patients experiencing TEAEs or drug-related TEAEs.

ACKNOWLEDGMENTS

The authors would like to extend gratitude to the patients and site staff who were involved in the APeX-P study. Medical writing support was provided by Sean Hubbert PhD of Oxford PharmaGenesis, part of the Klick Health family, funded by BioCryst Pharmaceuticals, Inc.

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