Berotralstat Decreased HAE Attacks Treated with On-Demand Therapy or Utilising Professional Care in Paediatric Patients Aged 2 to <12 years: APeX-P Results Through 48 Weeks

D2.498

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INTRODUCTION

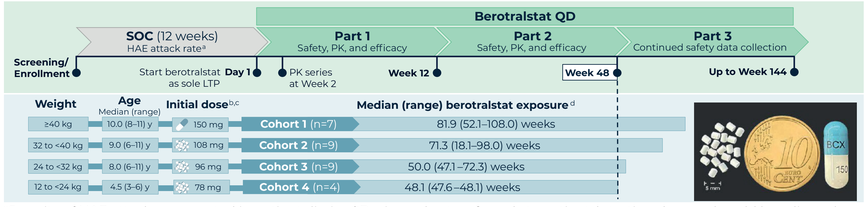
- Hereditary angioedema (HAE) is a rare autosomal-dominant disorder that can be treated with long-term prophylactic (LTP) medications to reduce the frequency, duration, and severity of angioedema attacks.[1]
- However, most currently approved prophylactic treatments for children aged <12 years require parenteral administration, which can be especially challenging in paediatric patients.[2] There is therefore an unmet need for oral LTP treatments for this population.
- Berotralstat, an oral small-molecule plasma kallikrein inhibitor approved for LTP of HAE in adults and adolescents aged ≥12 years, has recently been approved in the USA for children aged 2 to <12 years.[3]
- Here, we present an updated analysis of 48-week data from the ongoing APeX-P clinical trial.

METHODS

- APeX-P (NCT05453968; EU CTN 2024-511257-22-00) is an ongoing, open-label study evaluating the pharmacokinetics, efficacy and safety of berotralstat in patients with HAE aged 2 to <12 years and weighing ≥12 kg with HAE due to C1-inhibitor deficiency (HAE-C1INH) (**Figure 1**).
- Before berotralstat initiation, patients received standard of care (SOC) for 12 weeks that could include LTP, on-demand treatment, or both.[4]
- The rates of HAE attacks requiring on-demand treatment and the number of attacks which required professional care (comprising physician office, hospital emergency department, urgent care, and professional home care) were compared between 12 weeks of SOC and 48 weeks of berotralstat treatment.
- Patients were enrolled into one of four cohorts determined by body weight on Day 1 of berotralstat initiation; cohort 1 received berotralstat capsules, while cohorts 2, 3 and 4 received an oral pellet formulation.

Figure 1. APeX-P Study Design

Inclusion	Exclusion
· HAE-C1NH diagnosis · Age 2 to <12 years · Body weight ≥12 kg · Patient would benefit from oral LTP in the opinion of the investigator	· Any clinically significant medical condition or medical history that would interfere with patient safety or study participation



[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 an oral formulation. [d]All patients from Cohorts 1, 3, and 4, and n=7 of 9 enrolled patients in Cohort 2 completed at least 48 weeks of treatment.
HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema with C1-inhibitor deficiency; LTP, long-term prophylaxis; PK, pharmacokinetics; QD, once daily; SOC, standard of care; y, years.

ACKNOWLEDGEMENTS

The authors would like to extend gratitude to the patients and site staff involved in the APeX-P study. Medical writing support was provided by Adam Hargreaves PhD of Oxford PharmaGenesis, Oxford, UK, funded by BioCryst Pharmaceuticals, Inc.

FUNDING

This study was funded by BioCryst Pharmaceuticals Inc.

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RESULTS

Baseline characteristics

- In total, 29 participants were included in the study with a median (range) age of 8.0 (3–11) years; 48.3% of participants were female (**Table 1**).
- The median (range) age at HAE symptom onset was 2.0 (0.3–8.0) years, and 24 patients (82.8%) experienced symptom onset before the age of 6 years.
- This updated interim analysis comprises all 29 enrolled participants, of whom 27 (93.1%) completed at least 48 weeks of berotralstat treatment.

Table 1. Patient Baseline Demographics

	Total (N=29)
Age at screening (years)	
Mean (SD)	8.3 (2.1)
Median (range)	8.0 (3–11)
Age at symptom onset (years)	
Mean (SD)	2.9 (2.3)
Median (range)	2.0 (0.3–8)
Age at diagnosis (years)	
Mean (SD)	2.6 (2.3)
Median (range)	2.0 (0.2–10)
Race[a], n (%)	
White	22 (75.9)
Unknown	7 (24.1)
Sex at birth, n (%)	
Male	15 (51.7)
Female	14 (48.3)

[a]Some sites in France reported "Unknown" for race due to local regulations.
SD, standard deviation.

Table 2. TEAEs Occurring in ≥3 Patients

TEAEs[a]	Total (N=29) n (%)
Nasopharyngitis	10 (34.5)
Upper respiratory tract infection	8 (27.6)
Vomiting	5 (17.2)
Headache	4 (13.8)
Cough	3 (10.3)
Gastroenteritis	3 (10.3)
Viral upper respiratory tract infection	3 (10.3)

[a]The safety data include the entire duration of berotralstat exposure as of the data cut-off.
TEAE, treatment-emergent adverse event.

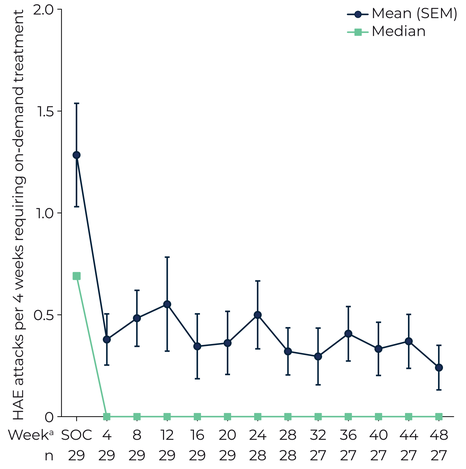
Safety

- The most common treatment-emergent adverse events (TEAEs) reported throughout the treatment period were nasopharyngitis, upper respiratory tract infection, vomiting and headache (**Table 2**).
- Throughout the 48-week treatment period, there were no drug-related Grade 3 or 4 TEAEs, drug-related serious adverse events, deaths or discontinuations related to adverse events.

Berotralstat efficacy

- The adjusted HAE attack rate requiring on-demand treatment decreased by Week 4 of berotralstat treatment and was sustained through Week 48 (**Figure 2**).
  - The median (range) adjusted HAE attack rate requiring on-demand treatment decreased from 0.691 attacks/month (0–5.03) during the 12-week SOC period to 0.169 attacks/month (0–1.75) during the 48-week berotralstat treatment period.
- The number of HAE attacks requiring professional care decreased from 22 during the 12-week SOC period to 3 after 12 weeks of berotralstat treatment; this was sustained throughout the treatment period, with further reduction to 0 attacks requiring professional care during Week 37–48 (**Figure 3**).

Figure 2. Monthly HAE Attack Rate Requiring On-Demand Treatment



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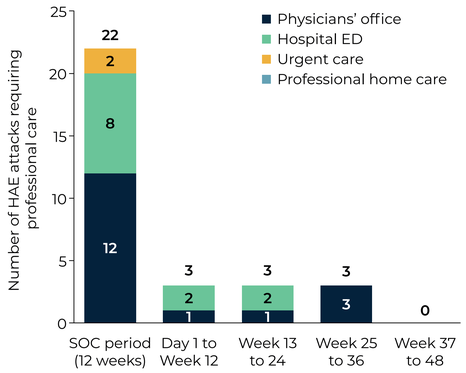
[a]Attack rates on treatment were calculated over a 4-week period since the previous time point.
HAE, hereditary angioedema; SEM, standard error of the mean; SOC, standard of care.

Figure 3. HAE Attacks Requiring Professional Care



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Note: there were four options for professional care including physician office, hospital ED, urgent care, and professional home care. No patients were recorded utilising professional home care.
ED, emergency department; SOC standard of care.

CONCLUSIONS

1. The ongoing APeX-P study is the largest trial of LTP in patients with HAE aged 2 to <12 years to date.
2. No significant safety concerns were identified over the 48-week treatment period.
3. In this updated analysis, treatment with berotralstat was associated with early and sustained reductions in rate and number of HAE attacks requiring on-demand treatment and requiring professional care, respectively.
4. These updated data from APeX-P continue to support a favourable benefit–risk profile for berotralstat LTP of HAE in a paediatric population.