Real-World Hereditary Angioedema Attack Rates Before and After Berotralstat Initiation Among Patients with C1 Inhibitor Deficiency (Type I/II) and ≥8 Attacks Per Month

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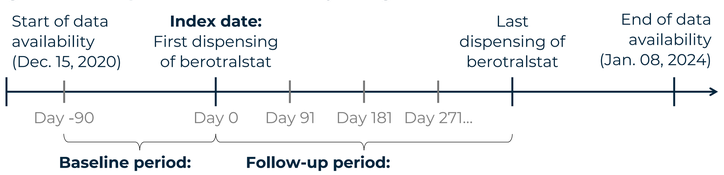
BACKGROUND

- Hereditary angioedema (HAE) causes painful, recurrent, and potentially life-threatening swelling of the skin and mucous membranes.[1]
- Berotralstat is a once-daily oral prophylaxis for the prevention of HAE attacks in patients aged 12 years and older.[2,3]
- The frequency of HAE attacks before berotralstat initiation contributes to the overall disease burden.[4]
- This study compared HAE attack rates before and after berotralstat initiation among patients with C1-inhibitor (C1-INH) deficiency (type I/II; HAE-C1-INH) and ≥8 attacks/month before berotralstat initiation.

METHODS

- This retrospective real-world study used Specialty Pharmacy data from Optime Care, Inc., the sole dispenser of berotralstat in the US, from Dec. 15, 2020, to Jan. 8, 2024.
- The follow-up period spanned from the index date (*first berotralstat dispensing date*) to the last berotralstat dispensing date; no patient assessment data were collected after the last berotralstat dispensing (**Figure 1**).

Figure 1. Retrospective Pre–Post Study Design



[a]To be included in the analysis of the first 90-day interval, patients were required to have ≥90 days of follow-up; to be included in the analysis of the second 90-day interval, patients were required to have ≥180 days of follow-up; and so on.

Study Outcomes

- Patient-reported HAE attacks were collected at berotralstat initiation and at each refill.
- Patients with ≥8 attacks/month at baseline were included (defined as ≥7.5 attacks/month, since calculated attack rates could have decimals).
- Mean and median monthly HAE attack rates were evaluated in the 90-day baseline period and in 90-day follow-up intervals.
  - The maximum rate of HAE attacks that patients could experience was assumed to be 1 attack per 2 days.
  - Baseline HAE attack rates were calculated based on the 90-day attack rate (divided by three to yield a 30-day attack rate) from the onboarding assessment.
  - In follow-up, the number of reported HAE attacks was the numerator, and the denominator was the minimum of (a) the time from the previous berotralstat shipment date, and (b) 30 days.

Statistical Analysis

- Mean monthly rates of HAE attacks at baseline and in the follow-up period (segmented into fixed 90-day intervals) were compared using mean differences, 95% confidence intervals (CIs), and *p*-values from generalized estimating equations (GEE) linear regression models with robust standard errors.
- The reasons for sample size decrease in the next interval were reported using frequencies and proportions for each 90-day interval.
  - Reasons for sample size decrease included berotralstat discontinuation (i.e., a gap in days' supply of ≥60 days) and end of study (i.e., patients reaching the end of the study period, Jan. 8, 2024, without evidence of discontinuation), no HAE attack report associated with dispensing, and discontinuation then re-initiation.

ACKNOWLEDGEMENTS

Editorial support was provided by Cristina Martinez, MA, of Groupe d'Analyse, Ltée, Montreal, QC, Canada, and Robert Schell, PhD, of Analysis Group, Inc, Menlo Park, CA, USA.

FUNDING

This study was funded by BioCryst Pharmaceuticals, Inc.

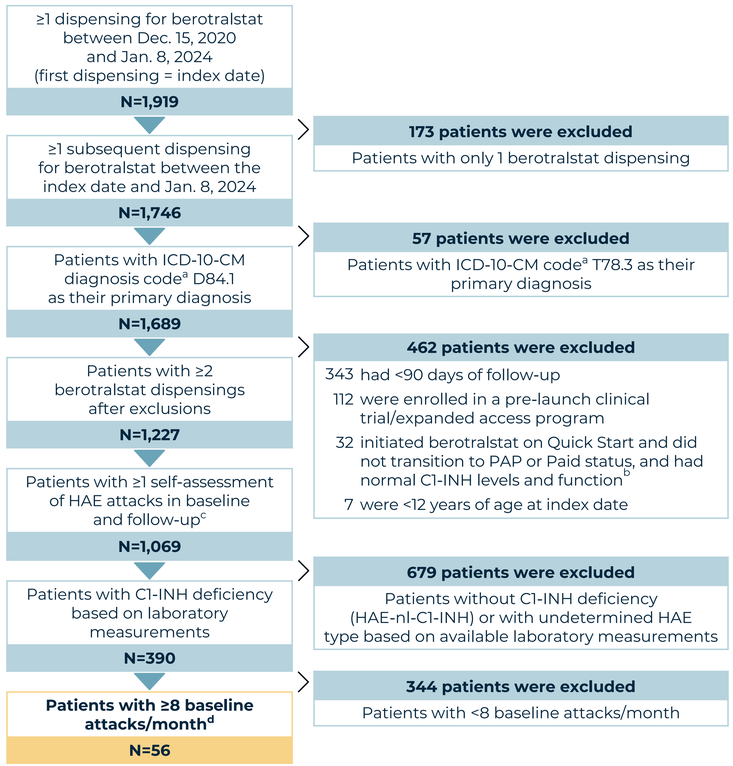
REFERENCES

1. Betschel S, et al. *Allergy Asthma Clin Immunol*. 2019;15(1):1-29. **2.** Berotralstat [package insert]. Durham, NC: November 2023. **3.** Powell J, et al. *Ann Pharmacotherapy*. 2022;56(4):488-493. **4.** Bork K, et al. *Allergy Asthma Clin Immunol*. 2021;17(40):1-14.

RESULTS

- The study population consisted of 56 patients with C1-INH deficiency and ≥8 baseline attacks/month who met the eligibility criteria (**Figure 2**).
- Mean age was 41 years, most patients were female (77%), and most patients were treated by an allergist/immunologist (95%) (**Table 1**).
- Patients had significantly lower HAE attack rates while on berotralstat during each 90-day follow-up interval (1.24–1.90 attacks/month) versus baseline (7.78–8.23 attacks/month) (**Figure 3**).
- The mean monthly attack rate reduction (95% CI) was 6.25 (5.63, 6.87) at 12 months and 6.43 (5.78, 7.09) at 18 months (both $p<0.001$) (**Figure 4**).

Figure 2. Eligibility Criteria and Patient Disposition



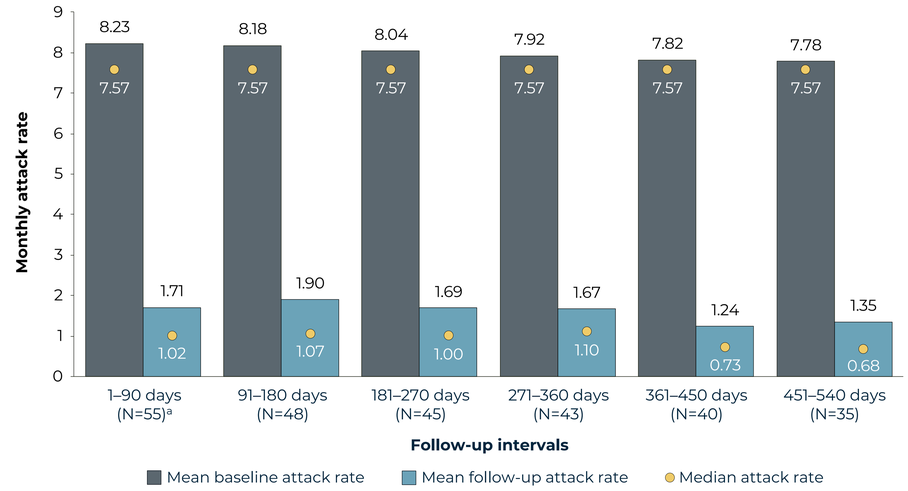
C1-INH, C1-inhibitor; HAE, hereditary angioedema; ICD-10-CM, *International Classification of Diseases, 10th Revision, Clinical Modification*; PAP, patient assistance program. [a]All patients had either D84.1 (defects in the complement system) or T78.3 (angioneurotic edema) as their primary diagnosis. [b]Patients excluded due to potential misdiagnosis. [c]158 patients excluded with no self assessment of HAE attacks in baseline or follow-up. [d]The sample size for the 1–90 interval (N=55) was smaller than the eligible study population (N=56) as 1 patient had ≥1 self-assessment of HAE attacks during follow-up but none during the first interval.

Table 1. Demographics and Clinical Characteristics

Characteristics	Patients (N=56)
Follow-up period, mean ± SD [median], days	663 ± 314 [721]
Demographics	
Age, mean ± SD [median], years	41.3 ± 17.2 [37]
Female, n (%)	43 (76.8)
Patient weight, mean ± SD [median], kg	80 ± 23 [76]
Healthcare practitioner specialty, n (%)	
Allergy/Immunology	53 (94.6)
Nurse practitioner	2 (3.6)
Other	1 (1.8)
Patient-reported prior LTP experience, n (%)[a]	15 (26.8)

LTP, long-term prophylaxis; SD, standard deviation. [a]Assessed any time before berotralstat initiation.

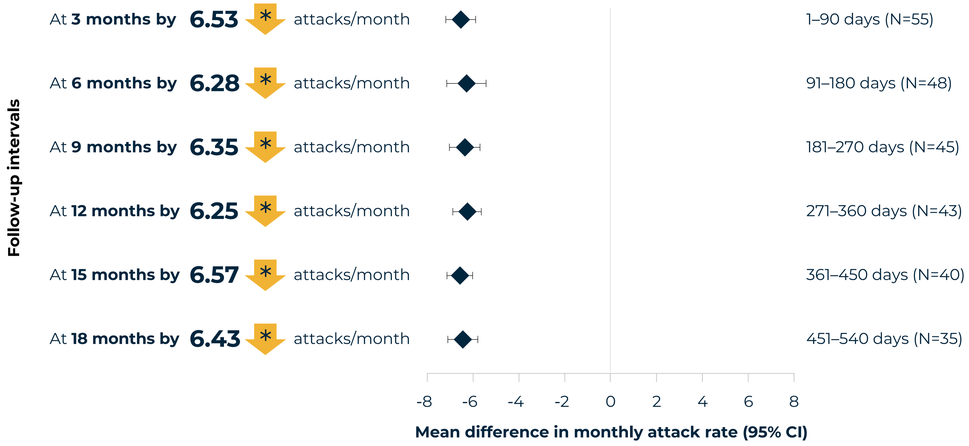
Figure 3. Monthly HAE Attack Rates (Mean and Median) Before and After Berotralstat Initiation



Reasons for sample size decrease in the next interval, n (%)[b]						
Discontinuation	4 (7.3)	2 (4.2)	2 (4.4)	2 (4.7)	3 (7.5)	1 (2.9)
End of study	2 (3.6)	1 (2.1)	1 (2.2)	1 (2.3)	1 (2.5)	1 (2.9)

HAE, hereditary angioedema. [a]The sample size for the 1–90 interval (N=55) was smaller than the eligible study population (N=56) as 1 patient had ≥1 self-assessment of HAE attacks during follow-up but none during the first interval. [b]Another reason for the decrease in sample size was the absence of HAE attack self-assessments linked to a berotralstat dispensing during an interval (0.0%–2.5%).

Figure 4. Reductions in HAE Attack Rates After Berotralstat Initiation



CI, confidence interval; HAE, hereditary angioedema. * Indicates $p<0.05$

Limitation

- A berotralstat dispensing does not necessarily indicate that the medication was consumed or taken as prescribed.

CONCLUSIONS

1. Patients with C1-inhibitor deficiency (type I/II; HAE-C1-INH) and ≥8 monthly baseline attacks reported statistically significant reductions exceeding 6 attacks/month after berotralstat initiation.
2. Treatment effectiveness was consistent and sustained through 18 months of follow-up.

Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2025 • May 13–16, 2025 • Montreal, QC, Canada