Real-World Attack Rate Reductions After Berotralstat Initiation Among Patients with Hereditary Angioedema with Normal C1-Inhibitor Stratified by Prior Long-Term Prophylaxis

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BACKGROUND AND OBJECTIVES

- Hereditary angioedema (HAE) is a rare genetic disease characterized by sudden, recurrent, and often painful swelling attacks involving the skin and mucous membranes, which can be potentially life-threatening.[1]
- Berotralstat is a targeted, once-daily, oral long-term prophylaxis (LTP) medication for the prevention of HAE attacks in adults and pediatric patients 2 years and older.[2,3]
- Evidence on HAE attack rates following berotralstat initiation among individuals with normal C1 esterase inhibitor (HAE-nC1INH) stratified by prior LTP experience is limited.
- This real-world study evaluated HAE attack rates among patients with HAE-nC1INH before and after initiating berotralstat stratified by prior LTP experience.

METHODS

- This retrospective study used Specialty Pharmacy data (December 15, 2020 – January 8, 2024) from Optime Care, Inc., the sole dispenser of berotralstat in the United States.
- The follow-up period extended from the index date (the first berotralstat dispensing) to the last berotralstat dispensing date during the study period; no patient assessment data were collected after the final berotralstat dispensing.

Study Outcomes

- Patients aged 12 years and older were categorized as LTP naïve or LTP experienced according to whether they self-reported using another LTP before initiating berotralstat.
- Patient self-assessments of HAE attacks were collected from the onboarding assessment at berotralstat initiation (based on prior 90 days) and from questionnaires administered at each berotralstat refill.
- Mean and median monthly HAE attack rates were evaluated in the 90-day baseline period and in each 90-day follow-up interval.
  - 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. The 30-day baseline attack rate was used if the 90-day baseline attack rate was missing.
  - 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, or (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 from one 90-day follow-up interval to the next were reported using frequencies and proportions.
  - Reasons for sample size decrease included berotralstat discontinuation (i.e., a gap in days' supply of ≥60 days); 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.

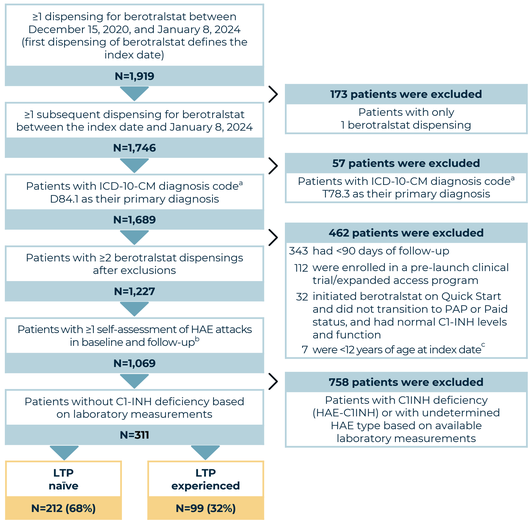
REFERENCES

1. Betschel S, et al. *Allergy, Asthma, & Clin Immunol.* 2019;15(1):1-29. **2.** Berotralstat [package insert]. Durham, NC: December 2025. **3.** Powell J, et al. *Ann Pharmacotherapy.* 2022;56(4):488-493.

RESULTS

- The study population consisted of 311 individuals with HAE-nC1INH, including 212 LTP naive patients and 99 LTP experienced patients who met the eligibility criteria (**Figure 1**).
- LTP naïve and experienced patients had a mean age of 48.9 and 46.4 years, respectively, both groups were predominantly female (75.0% and 82.8%), and most patients in each group were treated by an allergist/immunologist (86.3% and 96.0%) (**Table 1**).
- Among LTP naïve patients, mean HAE attack rates declined from 4.32–4.81 attacks/month during baseline to 1.17–2.07 attacks/month across 90-day follow-up intervals (**Figure 2**).
- Among LTP experienced patients, mean HAE attack rates declined from 4.07–4.57 attacks/month during baseline to 1.96–2.45 attacks/month across 90-day follow-up intervals (**Figure 3**).
- HAE attack rate reductions were statistically significant in every 90-day follow-up interval compared to the baseline period for LTP naïve and experienced patients (**Figure 4**).
- At 12 and 18 months, the mean monthly attack rate reduction (95% CI) was 3.65 (2.90, 4.39) and 2.75 (1.85, 3.66), respectively, for LTP naïve patients and 1.81 (1.04, 2.59) and 2.24 (1.29, 3.19) for LTP experienced patients (all p<0.001) (**Figure 4**).

Figure 1. Eligibility Criteria and Patient Disposition



C1INH, C1 esterase inhibitor; HAE, hereditary angioedema; ICD-10-CM, *International Classification of Diseases, 10th Revision, Clinical Modification*; LTP, long-term prophylaxis; PAP, patient assistance program. [a]All patients in the data had either D84.1 (defects in the complement system) or T78.3 (angioneurotic edema) as their primary diagnosis; however, only patients with D84.1 as their primary diagnosis were included in the sample. [b]158 patients were excluded with no self assessment of HAE attacks in baseline or follow-up. [c]Berotralstat was only approved for patients aged 12 and older during the study period.

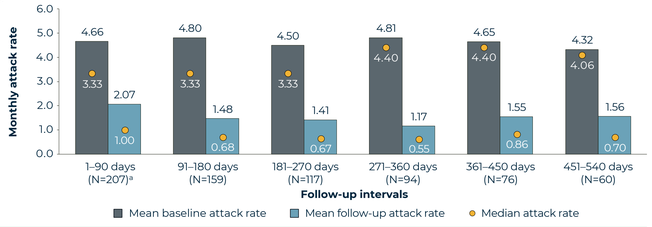
Table 1. Demographics and Clinical Characteristics

Characteristics	LTP Naïve (N=212)	LTP Experienced (N=99)
Follow-up period, mean ± SD [median], days	420 ± 283 [323]	544 ± 292 [532]
Demographics		
Age, mean ± SD [median], years	48.9 ± 17.3 [51]	46.4 ± 15.6 [47]
Female, n (%)	159 (75.0)	82 (82.8)
Patient weight, mean ± SD [median], kg	84 ± 21 [82]	83 ± 23 [79]
Healthcare practitioner specialty, n (%)		
Allergy/Immunology	183 (86.3)	95 (96.0)
Nurse practitioner	12 (5.7)	1 (1.0)
Other	17 (8.0)	3 (3.0)

Region, n(%)	LTP naïve	LTP experienced
South	102 (48.1)	45 (45.5)
Midwest	43 (20.3)	33 (33.3)
West	35 (16.5)	10 (10.1)
Northeast	27 (12.7)	10 (10.1)
Unknown	5 (2.4)	1 (1.0)

LTP, long-term prophylaxis; SD, standard deviation.

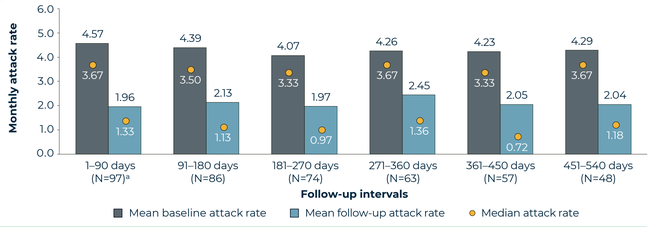
Figure 2. Monthly HAE Attack Rates (Mean and Median) Before and After Berotralstat Initiation Among Patients who were LTP Naïve



Reasons for sample size decrease in the next interval, n (%)[a,b]						
Discontinuation	24 (11.6)	12 (7.5)	5 (4.3)	9 (9.6)	2 (2.6)	–
End of study	26 (12.6)	26 (16.4)	16 (13.7)	9 (9.6)	13 (17.1)	–

HAE, hereditary angioedema; LTP, long-term prophylaxis. [a]The sample size for the 1–90 interval (N=207) was smaller than the eligible study population (N=212) as 5 patients had ≥1 self-assessment of HAE attacks during follow-up but none during the first interval. [b]Other reasons for sample size decrease were no HAE attack report associated with dispensing in interval (0.0%–1.7%) and discontinuation and later re-initiation (0.0%–2.5%).

Figure 3. Monthly HAE Attack Rates (Mean and Median) Before and After Berotralstat Initiation Among Patients who were LTP Experienced



Reasons for sample size decrease in the next interval, n (%)[a,b]						
Discontinuation	6 (6.2)	9 (10.5)	2 (2.7)	3 (4.8)	3 (5.3)	–
End of study	4 (4.1)	4 (4.7)	10 (13.5)	3 (4.8)	7 (12.3)	–

HAE, hereditary angioedema; LTP, long-term prophylaxis. [a]The sample size for the 1–90 interval (N=97) was smaller than the eligible study population (N=99) as 2 patients had ≥1 self-assessment of HAE attacks during follow-up but none during the first interval. [b]Other reasons for sample size decrease were no HAE attack report associated with dispensing in interval (0.0%–2.1%) and discontinuation and later re-initiation (0.0%–1.2%).

Figure 4. Reductions in HAE Attack Rates After Berotralstat Initiation for LTP Naïve and Experienced Subgroups

CI, confidence internal; HAE, hereditary angioedema; LTP, long-term prophylaxis. * Indicates $p<0.05$.

Limitations

- The presence of a berotralstat dispensing in the data does not indicate that the medication was consumed or taken as prescribed.
- Prior experience with LTPs other than berotralstat was defined based on self-reported medication use, which could be subject to recall bias or incomplete reporting.

CONCLUSION

This real-world study among patients with HAE-nC1INH observed significant, sustained reductions in HAE attack rates after berotralstat initiation regardless of prior LTP treatment history.

FUNDING

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