Reductions in Hereditary Angioedema Attacks among Patients with C1 Esterase Inhibitor Deficiency who Switched from Another Long-Term Prophylaxis to Berotralstat

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William R. Lumry,[1] Tracy Yee,[2] Jonathan A. Bernstein,[3] Sean D. MacKnight,[4] Robert C. Schell,[5] Yixin Yang,[5] François Laliberté,[4] Sandra Nestler-Parr,[2] Patrick Gillard,[2] Joshua S. Jacobs[6]

[1]Allergy and Asthma Research Associates, Dallas, TX, USA; [2]BioCryst Pharmaceuticals, Inc., Durham, NC, USA; [3]Department of Internal Medicine, University of Cincinnati, Cincinnati, OH, USA; [4]Groupe d'analyse SRI, Montreal, QC, Canada; [5]Analysis Group, Inc., Menlo Park, CA, USA; [6]Allergy and Asthma Medical Group of the Bay Area, Walnut Creek, CA, USA

BACKGROUND

- Hereditary angioedema (HAE) is a rare genetic disease characterized by sudden, recurrent, and often painful swelling attacks involving the skin and mucous membranes, which are potentially life-threatening.[1]
- Berotralstat is the only targeted, once-daily, oral long-term prophylaxis (LTP) medication for the prevention of HAE attacks in patients aged 12 years and older, and in pediatric patients aged 2 years and older in the United States (US).[2,3]
- Prior analysis of APeX-2 trial data demonstrated reductions in mean HAE attack rates among US patients with HAE with C1 esterase inhibitor deficiency (HAE-C1INH; type 1 or 2) treated with berotralstat,[4] with APeX-S reporting sustained low attack rates after switching from other injectable LTPs.[5]
- This real-world study compared HAE attack rates before and after initiation of berotralstat among patients with HAE-C1INH who switched from a prior LTP.

METHODS

Data Source and Study Design

- This real-world, retrospective study used Specialty Pharmacy data (December 3, 2020 – September 10, 2025) from Optime Care, Inc., the sole dispenser of berotralstat in the US.
- The follow-up period extended from the index date (first berotralstat dispensing) to the last berotralstat dispensing date; no patient assessment data were collected thereafter.
- Patients with HAE-nC1INH ≥12 years were categorized as switching from a prior non-berotralstat LTP if they self-reported use of ≥1 non-berotralstat LTP prior to index and stopped their last non-berotralstat LTP (defined as the LTP with the latest stop date) within the 60 days before or after the index date.

Study Outcomes and Statistical Analysis

- Patient self-assessments of HAE attacks were collected from the onboarding assessment at berotralstat initiation 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 the follow-up period (segmented into fixed 90-day intervals) up to 3 years.
  - The maximum rate of HAE attacks that patients could experience was assumed to be 1 attack per 2 days.
  - Baseline HAE monthly attack rates were calculated from the onboarding assessment as the 90-day attack rate divided by three. The 30-day baseline attack rate was used if the 90-day baseline attack rate was missing.
  - To allocate attacks into fixed 90-day follow-up intervals, the recall period for the reported number of HAE attacks was the minimum of (a) the time from the previous self-assessment date, or (b) 30 days. The monthly rate of attacks was calculated as the number of attacks in each 90-day interval divided by three.
- Mean monthly HAE attack rates 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.
- To be included in the analysis of a given 90-day follow-up interval, patients were required to have HAE attack self-assessment data in the interval and a follow-up period extending through the interval. These criteria were further broken down to report reasons for sample size change in the next interval using frequencies and proportions for each 90-day interval.
  - Reasons for sample size change 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, Sept. 10, 2025, without evidence of discontinuation), no HAE attack report associated with dispensing, and discontinuation then re-initiation.

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FUNDING

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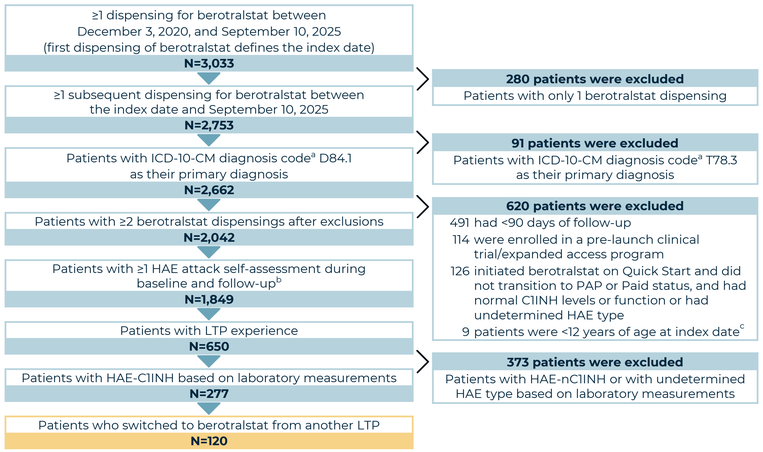
RESULTS

- The eligible study population consisted of 120 individuals with HAE-C1INH who switched to berotralstat from another LTP (**Figure 1**).
- Patients had a mean age of 42.5 years and over half (55.8%) were female (**Table 1**).
- Most patients switched from lanadelumab (37.5%) or SC-pdC1INH (26.7%) (**Figure 2**).
- Mean baseline attack rates were 1.77, 1.54, and 1.82 attacks/month among patients at 12, 24, and 36 months, respectively (**Figure 3**).
- HAE attack rate reductions were statistically significant in every 90-day follow-up interval compared to the baseline period (**Figure 4**).
- At 12, 24, and 36 months, mean monthly attack rate reductions (95% CIs) were 1.16 (0.55, 1.78), 0.88 (0.23, 1.53), and 1.22 (0.31, 2.13) attacks/month, respectively (all p<0.05) (**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; nC1INH, C1 esterase inhibitor normal; 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]193 patients were excluded without a self assessment of HAE attacks in baseline or follow-up. [c]Berotralstat was only approved for patients aged ≥12 years during the study period.

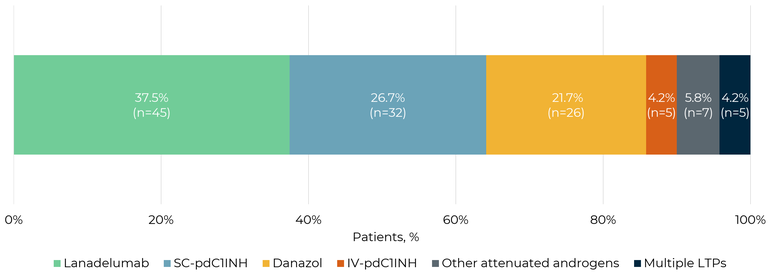
Table 1. Demographics and Clinical Characteristics

Characteristics	Patients (N=120)
Follow-up period, mean ± SD [median], days	751 ± 517 [660]
Demographics	
Age, mean ± SD [median], years	42.5 ± 19.9 [40]
Female, n (%)	67 (55.8)
Patient weight, mean ± SD [median], kg	85 ± 24 [81]
Healthcare practitioner specialty, n (%)	
Allergy/Immunology	110 (91.7)
Nurse practitioner	6 (5.0)
Other	4 (3.3)

Region	n (%)
South[a]	57 (47.5)
Midwest	24 (20.0)
West	30 (25.0)
Northeast	9 (7.5)

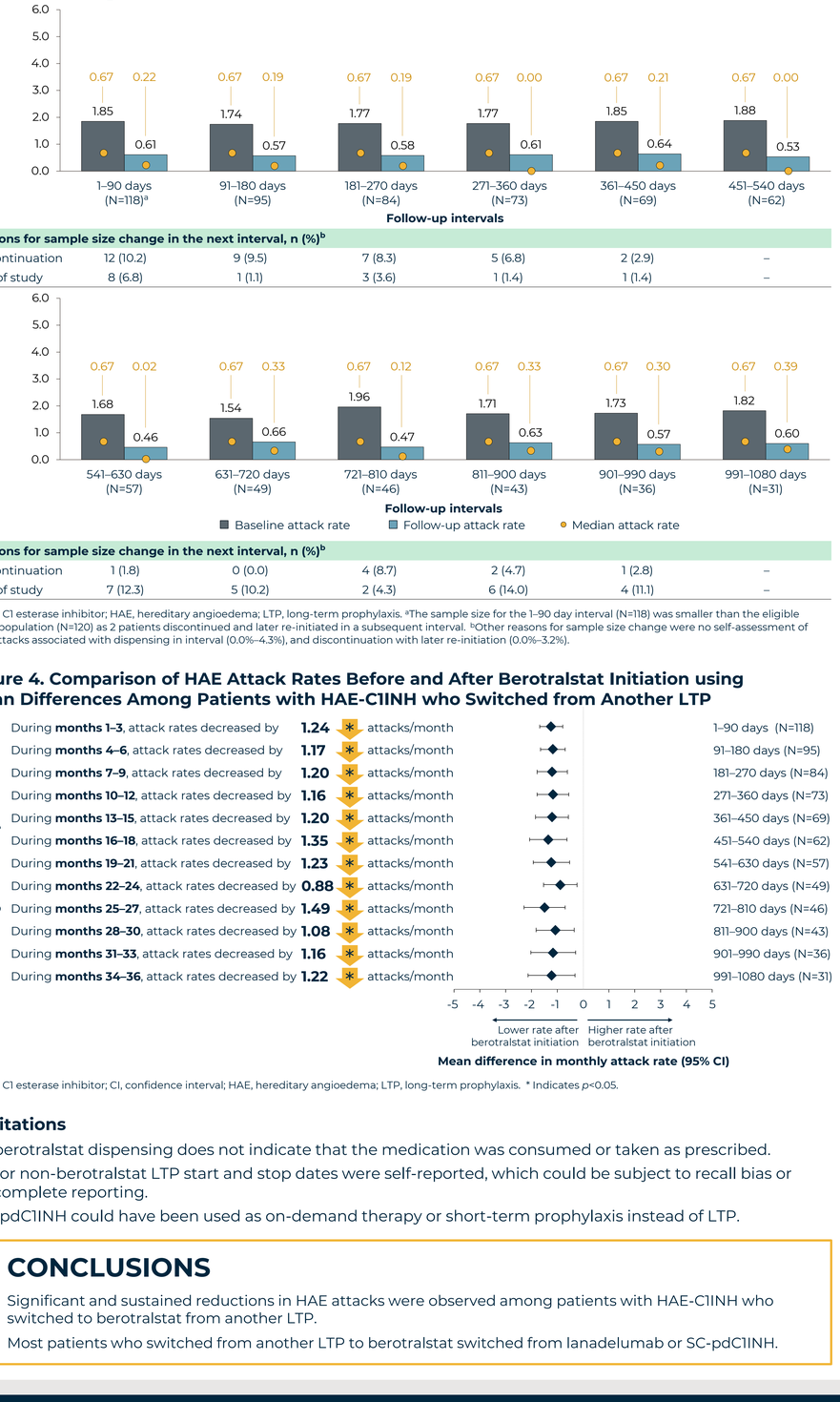
SD, standard deviation. [a]The South region includes patients from Puerto Rico and Guam.

Figure 2. LTP Agents used Prior to Switching to Berotralstat[a]



LTP, long-term prophylaxis; IV-pdC1INH, intravenous plasma-derived C1 esterase inhibitor; SC-pdC1INH, subcutaneous plasma-derived C1 esterase inhibitor. [a]Other attenuated androgens included stanozolol and oxandrolone. Multiple LTPs refers to patients with ≥2 LTP agents with the same stop date.

Figure 3. Monthly HAE Attack Rates (Mean and Median) Before and After Berotralstat Initiation Among Patients with HAE-C1INH who Switched from Another LTP



Reasons for sample size change in the next interval, n (%)[b]					
Discontinuation	12 (10.2)	9 (9.5)	7 (8.3)	5 (6.8)	2 (2.9)	–
End of study	8 (6.8)	1 (1.1)	3 (3.6)	1 (1.4)	1 (1.4)	–
Reasons for sample size change in the next interval, n (%)[b]						
Discontinuation	1 (1.8)	0 (0.0)	4 (8.7)	2 (4.7)	1 (2.8)	–
End of study	7 (12.3)	5 (10.2)	2 (4.3)	6 (14.0)	4 (11.1)	–

C1INH, C1 esterase inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis. [a]The sample size for the 1–90 day interval (N=118) was smaller than the eligible study population (N=120) as 2 patients discontinued and later re-initiated in a subsequent interval. [b]Other reasons for sample size change were no self-assessment of HAE attacks associated with dispensing in interval (0.0%–4.3%), and discontinuation with later re-initiation (0.0%–3.2%).

Figure 4. Comparison of HAE Attack Rates Before and After Berotralstat Initiation using Mean Differences Among Patients with HAE-C1INH who Switched from Another LTP

C1INH, C1 esterase inhibitor; CI, confidence interval; HAE, hereditary angioedema; LTP, long-term prophylaxis. * Indicates $p<0.05$.

Limitations

- A berotralstat dispensing does not indicate that the medication was consumed or taken as prescribed.
- Prior non-berotralstat LTP start and stop dates were self-reported, which could be subject to recall bias or incomplete reporting.
- IV-pdC1INH could have been used as on-demand therapy or short-term prophylaxis instead of LTP.

CONCLUSIONS

Significant and sustained reductions in HAE attacks were observed among patients with HAE-C1INH who switched to berotralstat from another LTP.

Most patients who switched from another LTP to berotralstat switched from lanadelumab or SC-pdC1INH.