Impact of Patient Recall and Reporting Intervals on Real-World Attack Reductions After Berotralstat Initiation in Hereditary Angioedema Patients without C1-Inhibitor Deficiency

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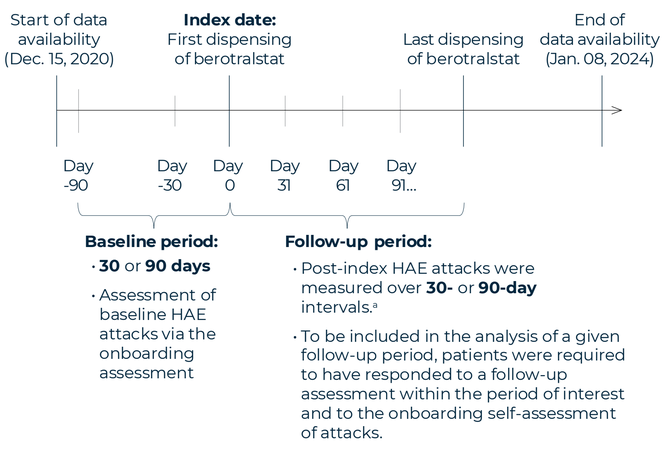
BACKGROUND

- Hereditary angioedema (HAE) is a rare disease characterized by painful, recurrent, and potentially life-threatening attacks of swelling of the skin and mucous membranes.[1]
- Some patients with HAE experience bradykinin-mediated swelling like HAE-C1-INH despite having normal C1-INH level and function (HAE-nl-C1-INH).[2]
- Prior studies have evaluated the real-world effectiveness of berotralstat, a targeted, once-daily oral medication for the prevention of HAE attacks,[3] on attack rate reductions over 90-day follow-up intervals and using a 90-day baseline recall period.
- To demonstrate the robustness of attack rate reduction findings, this study evaluated attack rate reductions by using a 30-day baseline recall period in addition to the 90-day baseline recall period among patients without C1-inhibitor deficiency (HAE-nl-C1-INH).

METHODS

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

Figure 1. Retrospective Pre–Post Study Design



HAE, hereditary angioedema. [a]To be included in the analysis of the first 30- or 90-day interval, patients were required to have ≥30 or ≥90 days of follow-up, respectively; to be included in the analysis of the second 30-day or 90-day interval, patients were required to have ≥60 or ≥180 days of follow-up; and so on.

Study Outcomes

- Patient-reported HAE attacks were collected at berotralstat initiation and at each refill.
- Mean and median monthly HAE attack rates were reported at 30- and 90-day baseline periods and in 30- and 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 30-day attack rate and 90-day attack rate (divided by 3 to yield a 30-day attack rate), respectively, 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 (30 or 90 days) and in the follow-up period (segmented into fixed 30- and 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.

RESULTS

- The study population consisted of 353 patients with ≥2 berotralstat dispensings, HAE-nl-C1-INH type classification based on laboratory measurements, and ≥1 self-assessment of HAE attacks in baseline and follow-up.
- Mean age was 48 years, most patients were female (78.5%), most patients visited an allergist/immunologist (88.4%), and nearly half of patients resided in the South; the mean follow-up period was 398 days (**Table 1**).
- Patients had significantly lower HAE attack rates while on berotralstat during each 30-day follow-up interval (1.68–2.53 attacks/month) versus baseline (5.23–5.63 attacks/month) and during each 90-day follow-up interval (1.63–2.04 attacks/month) versus baseline (4.30–4.66 attacks/month) (**Figure 2**).
- Mean monthly attack rate reductions (95% CI) using 30-day follow-up intervals and a 30-day baseline recall period were -3.75 (-4.43, -3.06) at 12 months (i.e., 331– 360-day interval) and -3.26 (-4.21, -2.32) at 18 months (i.e., 511–540-day interval; both $p<0.001$) (**Figure 3**).
- Using 90-day follow-up intervals and a 90-day baseline recall period, mean monthly attack rates reduced by -2.91 (-3.47, -2.35) at 12 months (i.e., 271–360-day interval) and -2.53 (-3.18, -1.87) at 18 months (i.e., 451–540-day interval; both $p<0.001$) (**Figure 3**).

Table 1. Demographics and Clinical Characteristics

Characteristics	Patients (N=353)
Follow-up period, mean ± SD [median], days	398 ± 301 [320]
Demographics	
Age, mean ± SD [median], years	48.1 ± 16.8 [49]
Female, n (%)	277 (78.5)
Patient weight, mean ± SD [median], kg	84 ± 22 [82]
Region, n (%)	
South	168 (47.6)
Midwest	83 (23.5)
West	54 (15.3)
Northeast	42 (11.9)
Unknown	6 (1.7)
Healthcare practitioner specialty, n (%)	
Allergy/Immunology	312 (88.4)
Nurse practitioner	18 (5.1)
Other	23 (6.5)

SD, standard deviation.

Figure 2. Mean and Median Hereditary Angioedema Attack Rates Before and After Berotralstat Initiation

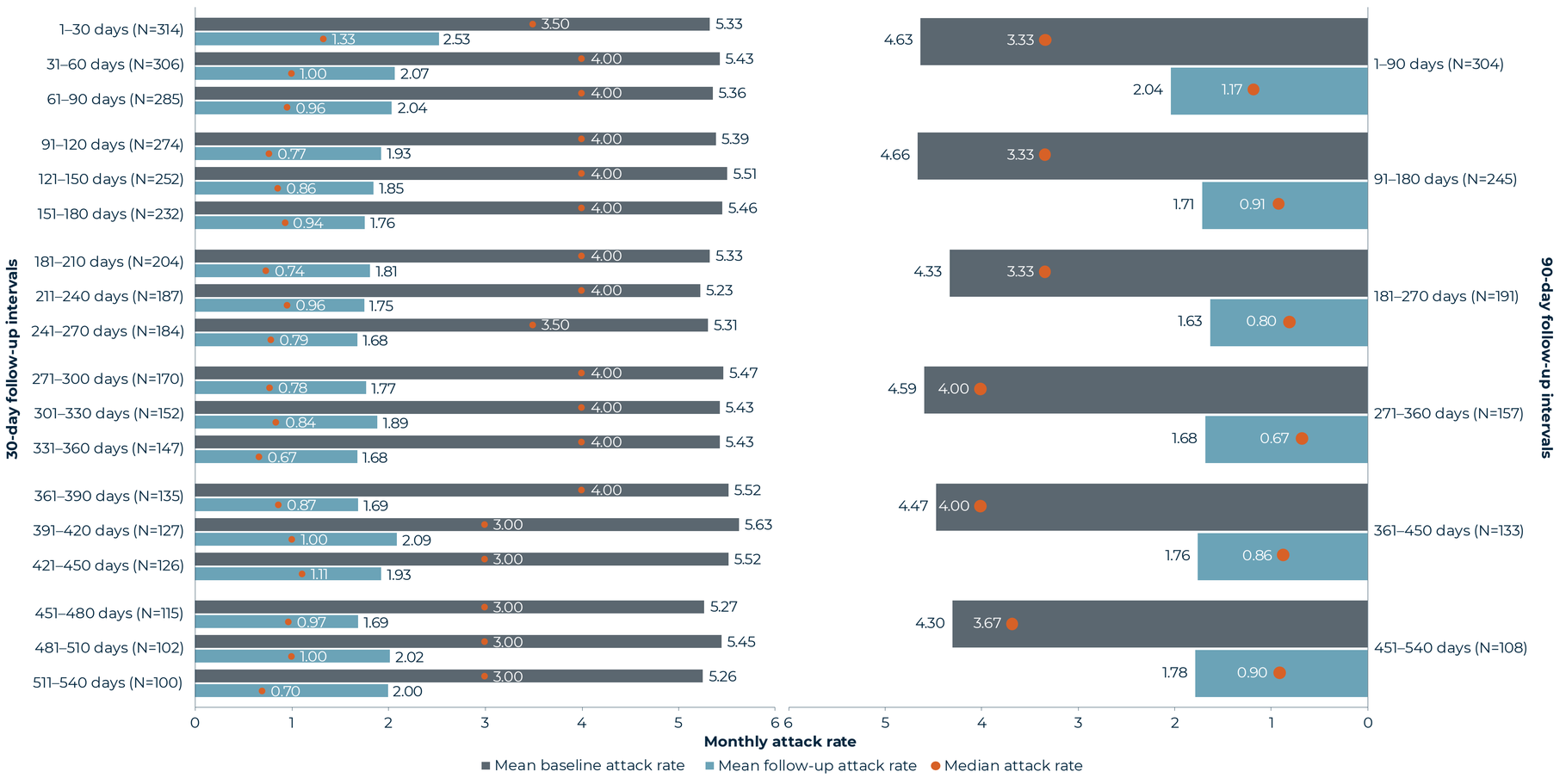
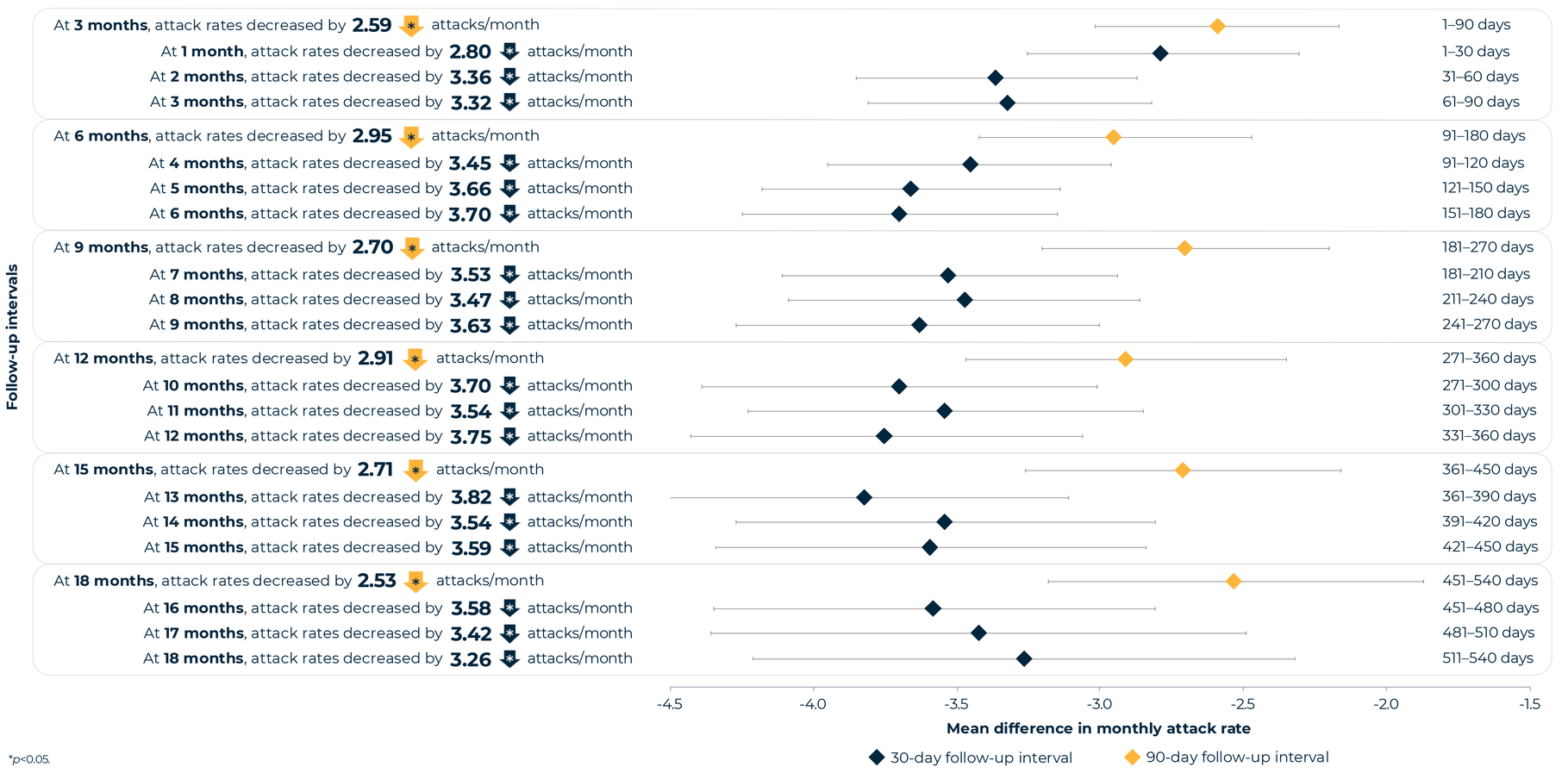


Figure 3. Reductions in Hereditary Angioedema Attack Rates After Berotralstat Initiation



*$p<0.05$.

Limitations

- Patients may have interpreted the definition and distinction between HAE attacks differently, as they were self-reported.
- The presence of a berotralstat dispensing in the data does not indicate that the medication was consumed or that it was taken as prescribed.

CONCLUSIONS

1. Berotralstat was associated with statistically significant and sustained reductions in HAE attack rates through 18 months following berotralstat initiation among patients without C1-inhibitor deficiency in the US.
2. This study observed statistically significant, sustained reductions in HAE attack rates after berotralstat initiation, regardless of the baseline timeframe of measurement (30-day or 90-day recall period) or follow-up timeframe of measurement (30-day or 90-day intervals). Higher baseline attack rates and larger attack reductions were observed when using 30-day recall periods, potentially due to better recall accuracy.

REFERENCES

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