Original Article

# Randomized Trial of the Efficacy and Safety of Berotralstat (BCX7353) as an Oral Prophylactic Therapy for Hereditary Angioedema: Results of APeX-2 Through 48 Weeks (Part 2)

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***What is already known about this topic?*** Berotralstat (BCX7353), a novel oral agent for prophylaxis of hereditary angioedema attacks, was shown to be effective and have a favorable benefit-to-risk profile over 24 weeks in part 1 of the APeX-2 study.

***What does this article add to our knowledge?*** Part 2 of the APeX-2 study confirmed the safety, tolerability, and effectiveness of berotralstat through 48 weeks of treatment. Patients who were rerandomized from placebo to berotralstat had substantial declines in hereditary angioedema attack rates.

***How does this study impact current management guidelines?*** As a once-daily oral therapy, berotralstat provides an effective alternative to current targeted prophylactic therapies for patients with hereditary angioedema that eliminates the treatment burdens associated with intravenous or subcutaneous administration.

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*Abbreviations used*
*AE- Adverse event*
*AE-QoL- Angioedema Quality of Life*
*C1-INH- C1 esterase inhibitor*
*HAE- Hereditary angioedema*
*QoL- Quality of life*
*SAE- Serious adverse event*
*TEAE- Treatment-emergent adverse event*
*TSQM- Treatment Satisfaction Questionnaire for Medication*

**BACKGROUND: Berotralstat (BCX7353) is a recently approved, oral, once-daily kallikrein inhibitor for hereditary angioedema (HAE) prophylaxis. In the APeX-2 trial, berotralstat reduced HAE attack rates over 24 weeks, with a favorable safety and tolerability profile.**
**OBJECTIVE: Evaluate berotralstat safety, tolerability, and effectiveness over 48 weeks.**
**METHODS: APeX-2 is a phase 3, parallel-group, multicenter trial (NCT03485911) in patients with HAE due to C1 esterase inhibitor deficiency. Part 1 was double-blind and placebo-controlled, with patients randomized to 24 weeks of berotralstat 150 mg, 110 mg, or placebo. In part 2, patients continued berotralstat the same dose or, if initially randomized to placebo, were rerandomized to berotralstat 150 mg or 110 mg through weeks 24 to 48. The primary end point was safety and tolerability.**
**RESULTS: One hundred eight patients received 1 or more doses of berotralstat in part 2. Treatment-emergent adverse events (TEAEs) occurred in 30 of 39 patients (77%) in the placebo group during part 1, and 25 of 34 patients (74%) re-randomized from placebo to berotralstat 110 mg or 150 mg in part 2, with drug-related TEAEs in 13 of 39 (33%), and 11 of 34 (32%) in the same groups. Most TEAEs were mild or moderate, with no serious drug-related TEAEs. The most common TEAEs were upper respiratory tract infections, abdominal pain, diarrhea, and vomiting. Mean (±standard error of the mean) monthly attack rates at baseline and week 48 were 3.06 (±0.25) and 1.06 (±0.25) in the berotralstat 150mg 48-week group and 2.97 (±0.21) and 1.35 (±0.33) in the berotralstat 110mg 48-week group.**
**CONCLUSIONS: The safety, tolerability, and effectiveness of berotralstat were maintained over 48 weeks of treatment.**  **(J Allergy Clin Immunol Pract 2021;■:■-■)**

***Key words:*** *Hereditary angioedema; HAE; Berotralstat; BCX7353; Prophylaxis; Phase 3 trial; Kallikrein inhibitor; Oral therapy; C1 inhibitor*

## INTRODUCTION

Hereditary angioedema (HAE) due to C1-INH (C1 esterase inhibitor) deficiency is a rare genetic disorder that results from mutations in the *SERPING1* gene. The primary manifestations are recurrent, unpredictable, and potentially disabling or life-threatening angioedema attacks in the skin or mucosa.[1-4] Hereditary angioedema causes a significant burden on patients and impacts quality of life (QoL) for patients and their families.[5-11]

Management of HAE has changed significantly in the past decade; earlier recognition of the disease and the expansion of available treatments have led to improved management. The increasing shift toward long-term prophylactic treatment to reduce the risk of attacks can decrease disease burden and have a positive impact on quality of life.[12] Recent treatment guidelines recommend that prophylactic therapy should be individualized by considering factors such as attack frequency, lifestyle, and patient preferences.[13] Until recently, all available targeted prophylactic therapies were administered by either intravenous or subcutaneous injection, which impose a substantial treatment burden on patients and their caregivers such as challenges with needle use and self-administration.[12,14] Thus, there is a significant unmet need for HAE treatment options that are less burdensome than the available targeted parenteral prophylactic therapies. This need could be addressed with an oral medication that is efficacious and well tolerated, with a more favorable adverse effect profile than the existing oral agents.

Berotralstat (BCX7353) is a highly selective oral inhibitor of plasma kallikrein that was recently approved for the prevention of angioedema attacks in adults and children aged 12 years or older with HAE.[15] Four studies have provided data on the clinical efficacy and safety of berotralstat for HAE prophylaxis: the phase 2 APeX-1 trial (NCT02870972), 2 ongoing phase 3 trials—APeX-2 (NCT03485911) and APeX-J (NCT03873116)—and an ongoing long-term safety study, APeX-S (NCT03472040). In APeX-1, the rate of confirmed HAE attacks was significantly lower among patients receiving berotralstat than among those receiving placebo.[16] In both APeX-2 and APeX-J, the results from part 1 (the randomized, double-blind, placebo-controlled portions) demonstrated that berotralstat significantly reduced the rate of HAE attacks compared with placebo and was generally well tolerated.[17-20] Finally, no new safety signals have been seen in the ongoing APeX-S study.[21]

The APeX-2 trial part 2 evaluated the safety, tolerability, and effectiveness of berotralstat through an additional 24 weeks of blinded active berotralstat treatment. Here we report the results of part 2 of the APeX-2 trial.

## METHODS

### Trial design

The APeX-2 is a phase 3, parallel-group, multicenter, 3-part trial (Figure 1). The study is being conducted at 40 sites in 11 countries (Table E1; available in this article's Online Repository at www.jaci-inpractice.org). Part 1 was randomized, double-blind, and placebo-controlled with a 24-week treatment period that compared berotralstat 150 mg once-daily and berotralstat 110 mg once-daily with placebo. The detailed design and final results of part 1 are reported elsewhere.[19] Part 2 evaluated the safety and tolerability of berotralstat, as well as effectiveness, QoL, and patient satisfaction with medication, from week 24 through week 48. In part 2, patients randomized to placebo in part 1 were rerandomized 1:1 to blinded active treatment with either berotralstat 150 mg once-daily or berotralstat 110 mg once-daily. Patients initially randomized to active treatment in part 1 continued on the same dose of blinded active treatment. All patients, investigators, and site personnel remained blinded to treatment group allocation in part 2, although all participants were informed that patients would receive active therapy in part 2.

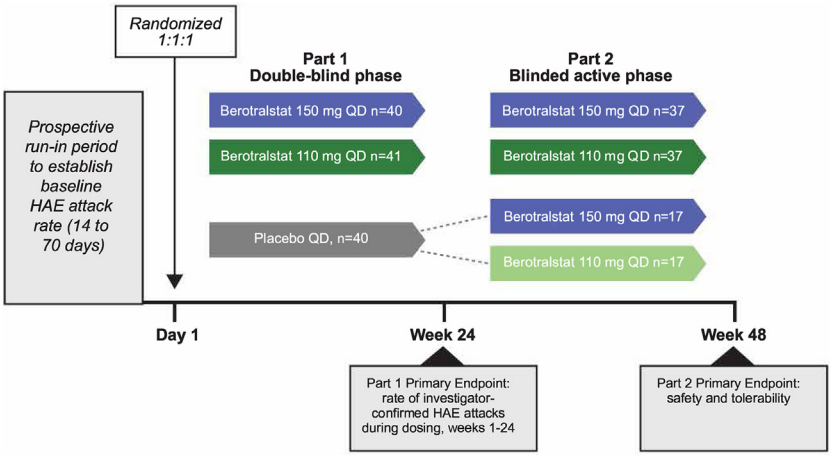



**FIGURE 1.** APeX-2 study design. *QD,* Every day.

The trial protocol and other study documents were reviewed and approved by the relevant regulatory authorities and independent ethics committees or institutional review boards before enrollment of any patients. All patients provided written informed consent (assent for adolescent patients) before undergoing any trial-related procedures. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation/Good Clinical Practice. An independent data monitoring committee provided review of safety data at prespecified intervals, with additional consultation or review as needed. This study was funded by BioCryst Pharmaceuticals, Inc.

## Patients

Patients were eligible for inclusion if they were 12 years of age or older (18 years or older at study sites in Europe), had a clinical diagnosis of type 1 or 2 HAE, were medically appropriate for on-demand treatment as the sole medical management for HAE during the study, and had experienced 2 or more investigator-confirmed HAE attacks within 56 days after the screening visit. A type 1 or 2 HAE diagnosis was defined as having a C1-INH functional level below 50% and a complement 4 (C4) level below the lower limit of normal, as assessed during the screening period. Patients with C1-INH functional level between 50% and 74% or C4 above the lower limit of normal could be enrolled if they were qualified based on alternative criteria, described in the Online Repository. All patients were required to have access to at least 1 approved on-demand therapy and were to treat HAE attacks in accordance with their usual treatment plan. Patients who completed treatment with the study drug in part 1 were eligible to continue into part 2.

## Treatments and randomization

Detailed information on treatment and randomization in part 1 is presented separately.[19]

Patients in the berotralstat 150mg or berotralstat 110mg groups who completed part 1 continued on the same dose in part 2. Patients in the placebo group who completed part 1 were rerandomized 1:1 to receive either berotralstat 150 mg once-daily or berotralstat 110 mg once-daily for part 2 in a blinded manner. Patients were randomized centrally using an interactive web response system (Veracity Logic, Chapel Hill, NC). No stratification was applied for part 2. The 1:1 randomization for part 2 (block size of 4) was generated using SAS v 9.3 software and uploaded to the interactive web response system.

## Assessments

Patients recorded the frequency, duration, location, functional impact, and any treatment of HAE attacks experienced in the previous 24 hours in an electronic diary daily. Investigators discussed each reported attack with the patient within 2 business days after the event.

The primary objective for part 2 was evaluation of long-term safety and tolerability. The primary end points included the number and proportion of subjects with treatment-emergent adverse events (TEAEs), discontinuations due to TEAEs, serious TEAEs, grade 3 or 4 TEAEs, or laboratory abnormalities, and rash. Relationship to the study drug was assessed by the investigator and TEAEs considered possibly, probably, or definitely related were classified as treatment related.

Secondary end points included the number and rate of investigator-confirmed HAE attacks, durability of response (attack rate trend over time), discontinuations due to lack of efficacy, and the durability of changes in Angioedema Quality of Life (AE-QoL) and Treatment Satisfaction Questionnaire for Medication (TSQM) scores. The AE-QoL is a validated, patient-reported outcome measurement that assesses QoL in 4 dimensions with a total of 17 items; a higher total score indicates greater QoL impairment (scale: 0−100 points; minimum clinically important difference for improvement is a reduction of 6 points).[22] The TSQM assesses treatment satisfaction across 4 domains (global satisfaction, effectiveness, side effects, and convenience) with scores ranging from 0 to 100; higher scores indicate greater satisfaction.[23]

Investigator-confirmed attacks were included in the analysis. Investigator confirmation was based on investigator review of diary data and discussion within 2 days of resolution of the attack between the patient and the investigator or an appropriately trained designee. Symptoms of swelling, including symptoms in the oropharyngeal or abdominal regions indicative of internal swelling, were required for an attack to be confirmed.

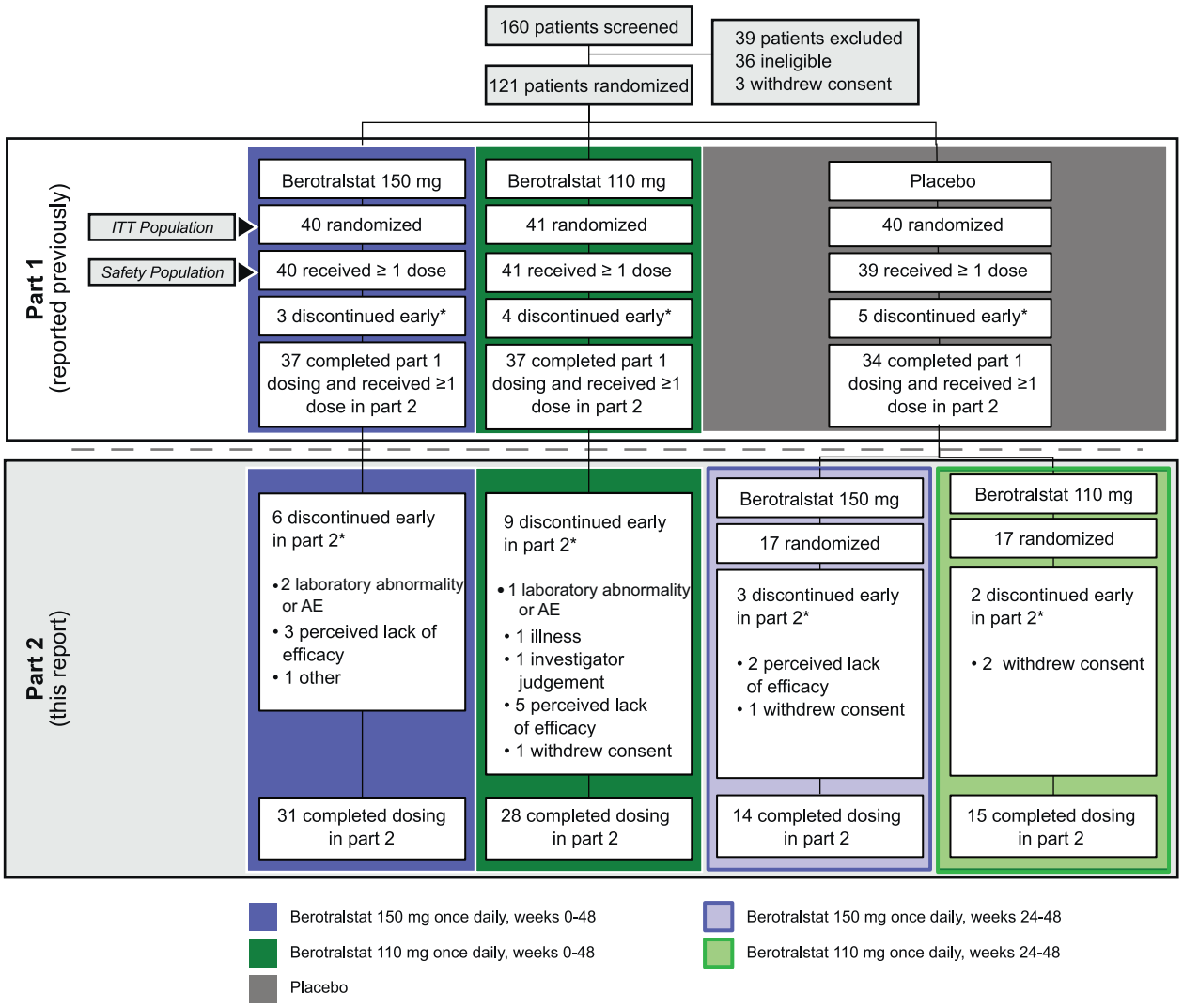



**FIGURE 2.** Patient disposition in APeX-2 parts 1 and 2. *ITT,* intention to treat. AE, adverse event *Discontinued study drug early; per protocol, some patients discontinued study drug but remained on-study through the end of the study part during which they discontinued.

## Statistical analyses

All prespecified analyses were detailed in the statistical analysis plan. Adverse events (AEs) are reported for the safety population, which includes all patients who received at least 1 dose of study medication. The investigator-confirmed attack rate was calculated for each month (a month was defined as a 28-day period). The total number of investigator-confirmed HAE attacks experienced in the period of interest was divided by the number of days in the study period and multiplied by 28 days/month to report the rate in attacks/month adjusted for the length of a month and the number of days during the period. If a subject discontinued during a given period, the attack rate was calculated through the date of discontinuation. Analyses of effectiveness and patient-reported outcomes were descriptive and were performed on all observed data at time points up to 48 weeks. A completers analysis was also conducted utilizing data from only those patients who received study treatment through week 48. The duration of investigator-confirmed attacks was calculated in hours, based on the start and stop time of the attack as reported by the subject. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Part 2 began with administration of the first dose of berotralstat dispensed after the week 24 visit.

# RESULTS

## Patients

Between March 14, 2018, and October 23, 2018, 160 patients were screened, of whom 121 were randomized and 120 were treated in part 1, as previously reported.[19] A total of 108 patients completed study drug dosing in part 1 and received at least 1 dose of berotralstat in part 2. Of these, 88 completed dosing in part 2. The last patient completed 48 weeks of dosing (parts 1 and 2) on September 25, 2019. Figure 2 summarizes patient dispositions in part 1 and details patient dispositions in part 2.

Among the 108 patients who were randomized in part 1 and continued in part 2, 94% were White, 68% were female, and the mean age was 41.6 years (range 12−72 years). Six patients were adolescents (range 12−17 years), and 8 were elderly (range 65−74 years). The mean (±SD) baseline HAE attack rate was 3.0 (±1.4). Patient baseline characteristics were generally similar

**TABLE I.** Baseline characteristics; ITT population: patients who transitioned to part 2

| Characteristic | Treatment | | | |
|---|---|---|---|---|
| | Berotralstat 150 mg (n = 37) | Berotralstat 110 mg (n = 37) | Berotralstat 150 mg after placebo (n = 17) | Berotralstat 110 mg after placebo (n =17) |
| Mean age at consent, y (SD) | 40.7 (14.2) | 39.1 (17.3) | 45.7 (14.8) | 44.8 (14.9) |
| Age at consent, n (%) | | | | |
| 12−17 y | 2 (5.4) | 2 (5.4) | 1 (5.9) | 1 (5.9) |
| 18−64 y | 34 (91.9) | 31 (83.8) | 14 (82.4) | 15 (88.2) |
| ≥65 y | 1 (2.7) | 4 (10.8) | 2 (11.8) | 1 (5.9) |
| Female sex, n (%) | 22 (59.5) | 27 (73.0) | 13 (76.5) | 11 (64.7) |
| Race, n (%)* | | | | |
| White | 35 (94.6) | 35 (94.6) | 15 (88.2) | 17 (100.0) |
| Black or African American | 1 (2.7) | 1 (2.7) | 1 (5.9) | 0 |
| Asian | 0 | 1 (2.7) | 0 | 0 |
| Other | 1 (2.7) | 0 | 1 (5.9%) | 0 |
| Mean weight at screening, kg (SD) | 89.1 (20.4) | 79.7 (21.9) | 89.2 (21.7) | 84.1 (23.6) |
| Mean BMI at screening, kg/m$^2$ (SD) | 30.8 (6.8) | 27.8 (7.5) | 30.8 (7.2) | 29.1 (7.0) |
| Region, n (%) | | | | |
| North America | 24 (64.9) | 29 (78.4) | 12 (70.6) | 12 (70.6) |
| Europe | 13 (35.1) | 8 (21.6) | 5 (29.4) | 5 (29.4) |
| Baseline investigator-confirmed attack rate, mean (SD) | 3.2 (1.6) | 3.0 (1.3) | 2.8 (1.4) | 2.9 (0.9) |
| ≥2 attacks/month | 29 (78.4) | 26 (70.3) | 10 (58.8) | 13 (76.5) |
| <2 attacks/month | 8 (21.6) | 11 (29.7) | 7 (41.2) | 4 (23.5) |
| Any past prophylactic treatment for HAE, n (%) | 29 (78.4) | 28 (75.7) | 12 (70.6) | 14 (82.4) |
| Any prior androgen use, n (%)† | 20 (54.1) | 17 (45.9) | 10 (58.8) | 12 (70.6) |
| Any prior prophylactic C1-INH use, n (%)‡ | 20 (54.1) | 14 (37.8) | 7 (41.2) | 7 (41.2) |
| Prior prophylactic treatment use within 30 d of screening, n (%) | 12 (32.4) | 8 (21.6) | 4 (23.5) | 6 (35.3) |

*BMI,* Body mass index; *C1-INh*, C1 esterase inhibitor; *ITT,* intent to treat (the ITT population included all patients who underwent randomization); *SD*, standard deviation.
*Race was self-reported.
†Prior androgen use was noted in the patients' HAE medical and medication history and included any of the following androgens (unspecified), oxandrolone, methyltestosterone, danazol, and stanozolol.
‡C1-INH includes plasma-derived and recombinant C1-INH and fresh frozen plasma.

**TABLE II.** Overall summary of TEAEs through week 48, safety population

| Number (%) of Patients with: | Up to 48 weeks exposure | | Up to 24 weeks exposure | | |
|---|---|---|---|---|---|
| | 150 mg (n = 40) | 110 mg (n = 41) | 150 mg after placebo (n = 17) | 110 mg after placebo (n = 17) | Placebo (n = 39) |
| Any AE | 38 (95.0) | 38 (92.7) | 12 (70.6) | 13 (76.5) | 30 (76.9) |
| Any drug-related AE | 17 (42.5) | 18 (43.9) | 7 (41.2) | 4 (23.5) | 13 (33.3) |
| Any SAE | 1 (2.5) | 1 (2.4) | 1 (5.9)* | 0 | 2 (5.1) |
| Any drug-related SAE | 0 | 0 | 0 | 0 | 0 |
| Any grade 3 or 4 AE | 3 (7.5) | 5 (12.2) | 1 (5.9) | 1 (5.9) | 3 (7.7) |
| Any drug-related grade 3 or 4 AE | 1 (2.5) | 3 (7.3) | 0 | 0 | 0 |
| Any AE leading to discontinuation of study drug | 3 (7.5) | 4 (9.8) | 0 | 0 | 1 (2.6) |
| GI abdominal AEs leading to discontinuation of study drug | 1 (2.5) | 2 (4.9) | 0 | 0 | 0 |
| Any investigator-identified rash† | 2 (5.0) | 0 | 0 | 0 | 0 |

*AE,* Adverse event; *GI,* gastrointestinal; *SAE,* serious adverse event
*Uterine leiomyoma; previously reported as occurring in part 1 in the placebo group.
†An investigator-identified rash is any AE that the investigator noted as an AE of special interest on the AE case report form.
GI abdominal AE is any AE with a preferred term within the Medical Dictionary for Regulatory Activities (MedDRA) v19.1 hierarchy under the High Level Group Terms of (1) GI signs and symptoms or (2) GI motility and defecation conditions. TEAEs were defined as any AE after initiation of study drug through wk 48 or the last dose of study drug + 30 d if the subject discontinued prior to wk 48. Detailed definitions are presented in the Online Repository.

across all treatment groups, except that patients in the placebo to berotralstat groups were older, and fewer women were enrolled in the berotralstat 150mg group (Table I).

## Safety

TEAEs were reported by 76 of 81 patients (94%) who were randomized to berotralstat in parts 1 and 2 (up to 48 weeks of

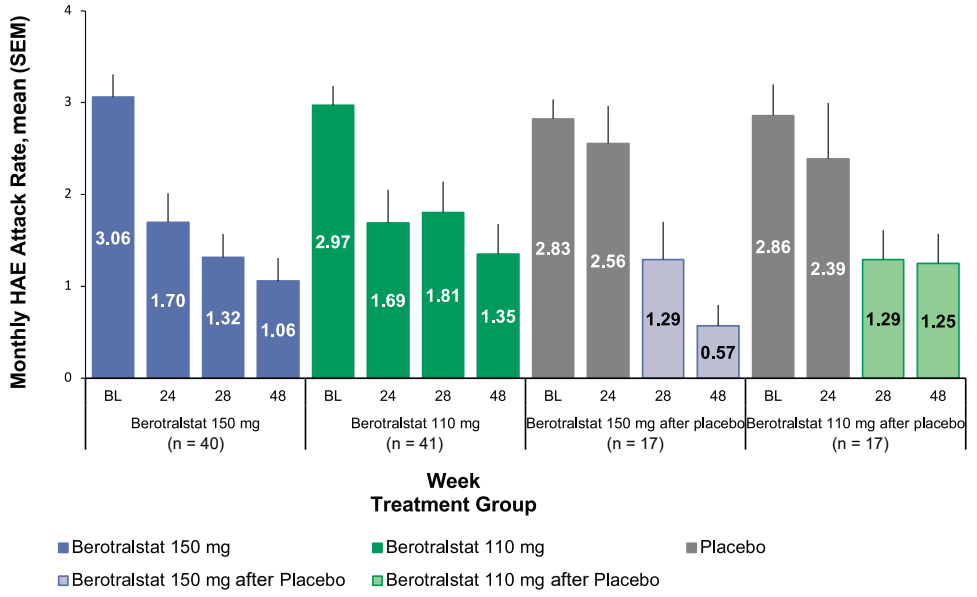



**FIGURE 3.** Mean (standard error of the mean [SEM]) investigator-confirmed HAE monthly attack rates at baseline (BL), 24 weeks, 28 weeks, and 48 weeks by treatment arm. Intention to treat (ITT) population. Error bars represent the SEM. Attack rates are for the 4 weeks preceding each visit.

exposure to berotralstat), by 30 of 39 patients (77%) randomized to placebo in part 1 (up to 24 weeks of exposure to placebo), and by 25 of 34 patients (74%) rerandomized from placebo to berotralstat in part 2 (up to 24 weeks of exposure to berotralstat). Table II summarizes the AEs reported. Most were mild or moderate in severity. The most common AEs (ie, those reported during parts 1 and 2 in ≥10% of patients in any treatment group) were upper respiratory tract infection, nausea, abdominal pain, dyspepsia, diarrhea, vomiting, headache, flatulence, gastroesophageal reflux disease, and back pain (Table E2; available in this article's Online Repository at www.jaci-inpractice.org). Drug-related AEs were reported by 35 of 81 patients (43%) who were randomized to berotralstat in parts 1 and 2 (up to 48 weeks of exposure to berotralstat), by 13 of 39 patients (33%) randomized to placebo in part 1 (up to 24 weeks of exposure to placebo), and by 11 of 34 patients (32%) rerandomized from placebo to berotralstat in part 2 (up to 24 weeks of exposure to berotralstat) (Table II). Ninety-one percent of the drug-related TEAEs were mild or moderate (grade 1 or 2) in severity.

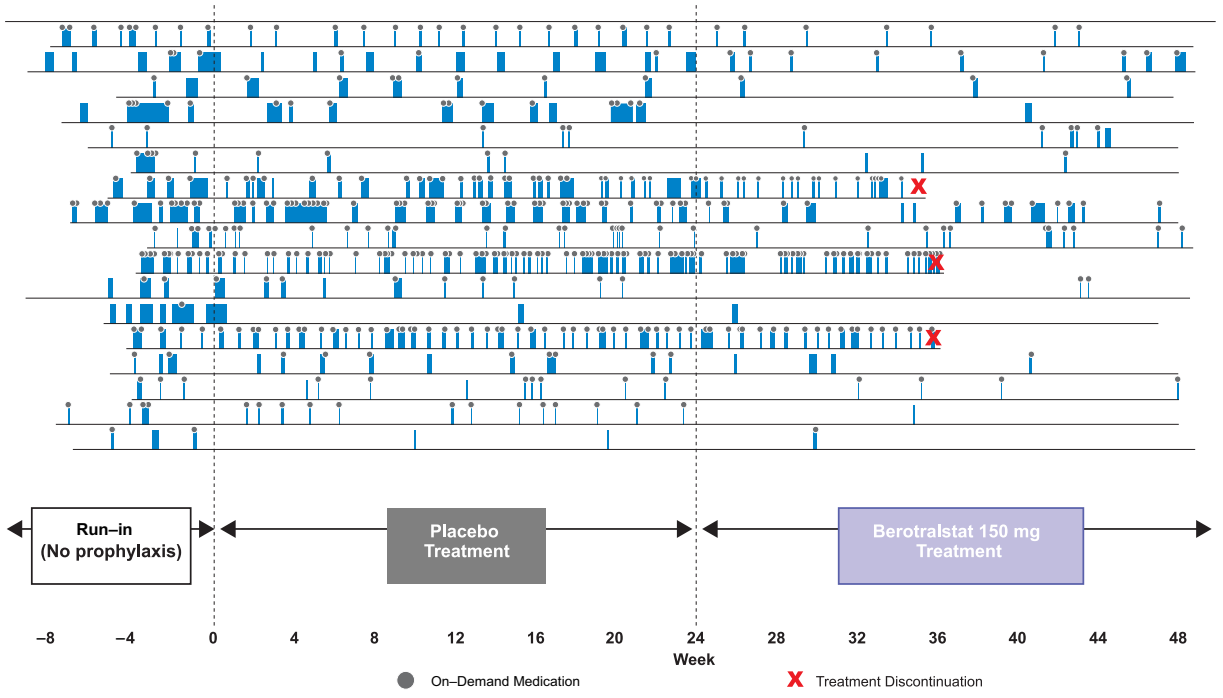
Nine percent of TEAEs were grade 3 or 4 in severity. Grade 3 or 4 TEAEs due to any cause were reported by 8 of 81 patients (10%) randomized to berotralstat in parts 1 and 2, 3 of 39 patients (8%) randomized to placebo in part 1, and 2 of 34 patients (6%) who were rerandomized from placebo to berotralstat for part 2. Details are presented in Table E3 (available in this article's Online Repository at www.jaci-inpractice.org). Of the 10 patients randomized to berotralstat who reported grade 3 or 4 AEs, 4 patients had a total of 5 events that were considered drug-related (all grade 3): 3 events previously reported in part 1, and 2 events of grade 3 anal incontinence in 1 patient receiving berotralstat 150 mg in part 2. No drug-related grade 4 AEs were reported.

Treatment-emergent serious adverse events (SAEs) occurred in 5 patients in parts 1 and 2: 4 patients previously reported in part 1 and 1 patient in part 2. Details of all SAEs occurring in the study are presented in the Table E3. In part 2, 1 patient in the berotralstat 150-mg group underwent medical observation; the patient was hospitalized according to the local standard of care for a routine screening procedure (radioactive iodine test) unrelated to HAE or treatment. There were no drug-related SAEs in any treatment group.

Seven patients receiving berotralstat discontinued study drug due to AEs through 48 weeks: 4 in part 1, and 3 in part 2 (2 patients receiving berotralstat 150 mg due to anal incontinence and palpitations/tachycardia; 1 patient receiving berotralstat 110 mg due to nausea). In part 2, 17 patients discontinued for reasons other than AEs (Figure 2), including 10 patients who discontinued for perceived lack of efficacy: 3 patients receiving berotralstat 150 mg, 5 patients receiving berotralstat 110 mg, and 2 patients who were rerandomized from placebo to berotralstat 150 mg.

## Effectiveness

Significant declines in the HAE attack rate were observed in part 1 as previously reported.[19] Attack rates declined further by the end of part 2 among patients receiving berotralstat 150 mg or berotralstat 110 mg for the entire 48-week dosing period (Figure 3). Mean attack rates (±standard error of the mean [SEM]) for the 150mg group declined from 3.06 (±0.25) attacks/month at baseline to 1.70 (±0.32) at week 24, 1.32 (±0.26) at week 28, and 1.06 (±0.25) at week 48. For the 110mg group, attack rates were 2.97 (±0.21) at baseline, 1.69 (±0.36) at week 24, 1.81 (±0.34) at week 28, and 1.35 (±0.33) at week 48. The HAE attack rates decreased in part 2 for patients who rerandomized from placebo to either dose of berotralstat. The magnitude of the decrease was similar to that observed in part 1 for patients originally randomized to berotralstat. In the placebo to berotralstat 150mg group, mean attack rates were 2.83 (±0.34) at baseline, 2.56 (±0.61) at week 24 (immediately

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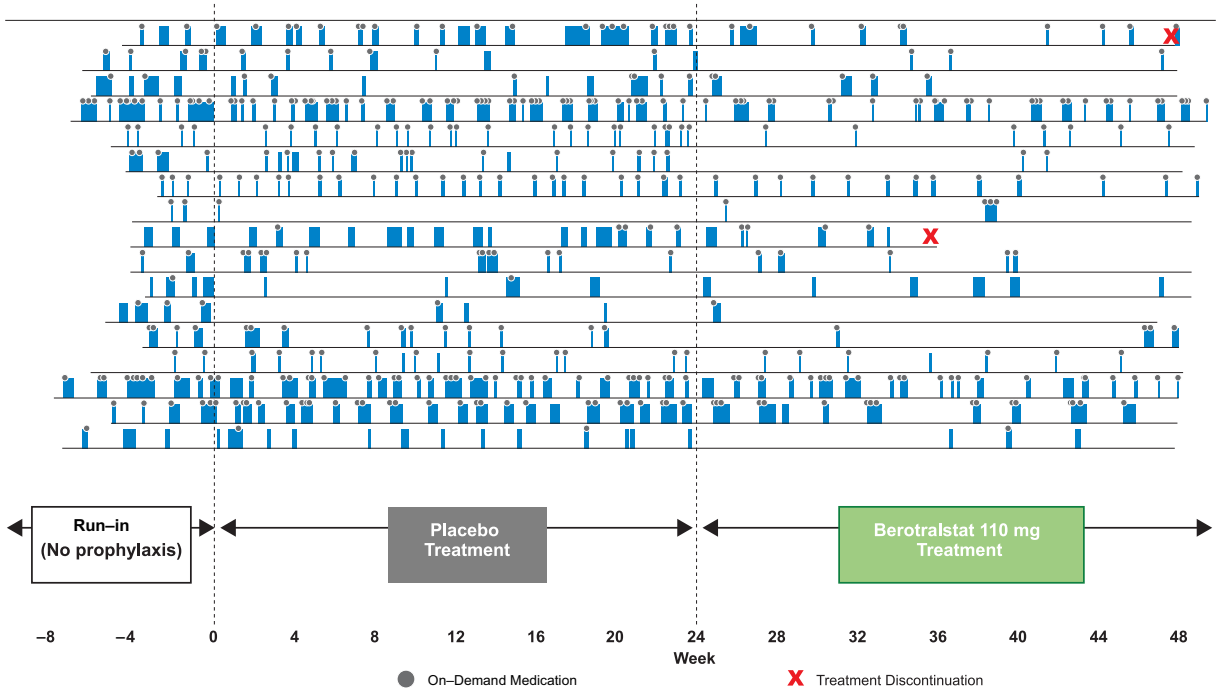


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**FIGURE 4.** Investigator-confirmed HAE attacks and use of on-demand medication. (**A**) Patients who transitioned to berotralstat 150 mg after placebo. (**B**) Patients who transitioned to berotralstat 110 mg after placebo. Each horizontal line represents 1 patient. Vertical blue bars represent HAE attacks and show the duration of each attack. Each dark gray dot above a blue bar represents use of on-demand therapy. Each red X at the end of a horizontal line represents treatment discontinuation.

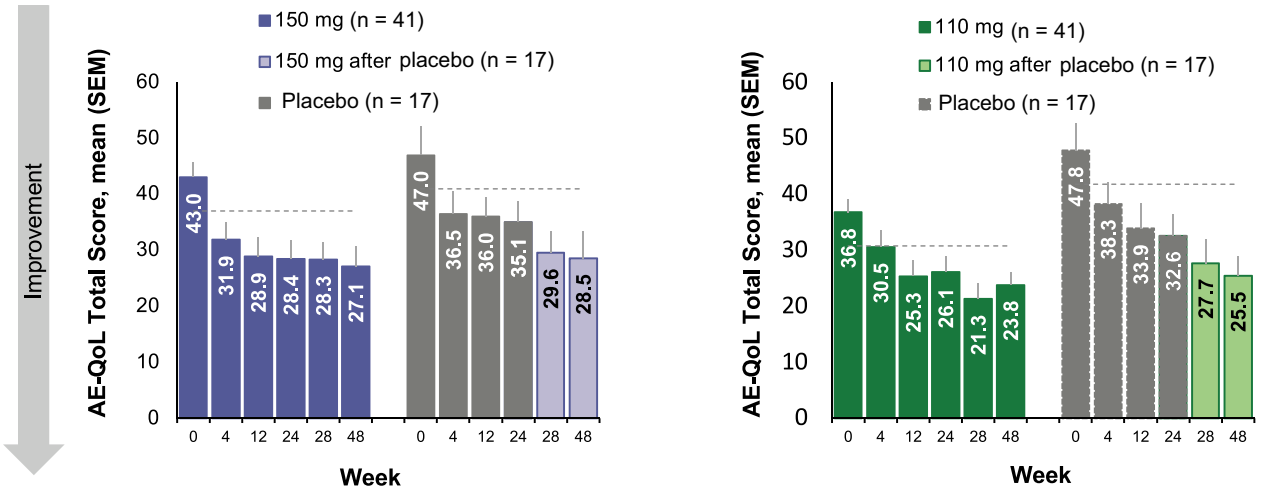


**FIGURE 5.** Mean (SEM) AE-QoL total score by visit week. A decrease represents improvement. Error bars represent the SEM. Dashed horizontal lines indicate the mimimally clinically important difference from baseline (week 0).

before starting berotralstat), 1.29 (±0.41) at week 28 (4 weeks after starting berotralstat), and 0.57 (±0.23) at week 48 (24 weeks after starting berotralstat). In the placebo to berotralstat 110mg group, mean attack rates were 2.86 (±0.21) at baseline, 2.39 (±0.41) at week 24, 1.29 (±0.25) at week 28, and 1.25 (±0.32) at week 48.

A completers analysis, including only patients who continued dosing with study treatment through the week 48 visit, was performed to address the potential for bias in secular trend in attack rate arising from differential rates of discontinuation. The completers analysis found results similar to the primary analysis results, with further reduction in attack rates from months 6 to 12, indicating that discontinuations had no meaningful impact on study results (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org).

All attacks during screening, part 1, and part 2, including frequency, duration, and use of on-demand treatment, are shown in Figure 4 for each patient who transitioned from placebo to berotralstat 150 mg or 110 mg in part 2. After the patients started berotralstat, the frequency and duration of HAE attacks and patients' use of on-demand HAE treatment generally declined.

### Patient-reported outcomes

Patients on berotralstat in parts 1 and 2 experienced an improvement in the AE-QoL total score, starting as early as week 4, which was sustained through week 48. For patients who were rerandomized from placebo to berotralstat, AE-QoL total scores improved after initiation of berotralstat (Figure 5). Sixty-seven percent of all berotralstat-treated patients achieved the minimum clinically important difference (MCID) at week 48. In addition to the assessment of QoL, the effect of berotralstat on patient satisfaction with treatment was evaluated using the TSQM, which showed improvements in global satisfaction in patients who were rerandomized from placebo to berotralstat (Figure E2; available in this article's Online Repository at www.jaci-inpractice.org).

## DISCUSSION

The APeX-2 trial evaluated berotralstat for HAE attack prophylaxis using a 3-part design: part 1 evaluated efficacy and safety by comparing 2 doses of berotralstat with a placebo control group, and part 2 evaluated safety, tolerability, and effectiveness without a control group to minimize patients' time on placebo. The long-term open-label extension phase of the study (part 3) is ongoing. Part 2 results confirm the safety and efficacy profiles observed for berotralstat in part 1. The trial enrolled patients with HAE who represent a wide spectrum of HAE disease burden and are likely to benefit with prophylaxis. The results are expected to be generalizable to this patient population.

No new safety signals were identified in part 2 of the trial. Berotralstat was well tolerated throughout the trial with no drug-related SAEs reported. The majority of AEs were mild or moderate. The rate of AEs reported in part 2 by patients in the berotralstat after placebo groups was similar to the rate reported by the same patient groups while receiving placebo in part 1. Over the entire 48-week trial, less than 10% of patients receiving berotralstat discontinued due to AEs. Note that patients who were randomized to berotralstat in part 1 had greater duration of exposure to berotralstat (48 weeks) than patients who were rerandomized from placebo to berotralstat at week 24 (24 weeks). This longer observation time would be expected to increase the number and subject incidence of TEAEs reported, and this should be considered when reviewing the data.

Among patients who completed 48 weeks of treatment, mean attack rates declined by 67% and 52% from baseline to week 48 in the berotralstat 150mg and 110mg groups respectively. In part 2 of the study, the reduction in attack rates observed in part 1 continued or declined further, particularly in the berotralstat 150mg group. The decrease in attack rate observed in part 2 in both berotralstat groups demonstrates a clear durability of response to treatment. The continued reduction in attack rates is an important goal in the treatment of HAE. Among patients who were rerandomized from placebo to berotralstat, the mean monthly attack rate declined and remained consistently low through the 24 weeks of berotralstat therapy in part 2 (week 48: 0.57 attacks/month, 150 mg; 1.25 attacks/month, 110 mg).

Berotralstat is a novel small molecule kallikrein inhibitor indicated as an oral prophylactic therapy to prevent HAE attacks in adults and children 12 years and older. Until berotralstat became available, all targeted prophylactic therapies had been

parenteral and could impose a treatment burden on patients and caregivers, with issues related to convenience and logistics such as refrigeration, transport and disposal of syringes and needles, and the skills and time required for the complex reconstitution and administration processes.[14,24] In addition, self-administration may be problematic for needle-phobic patients or those with venous access issues. A recent study found that the majority of patients receiving HAE prophylaxis agree that needles and the injection/infusion process are unpleasant, and many have "bad veins", injection site reactions, and/or find medication storage and preparation inconvenient.[24] Voice-of-the-patient research conducted by the U.S. Food and Drug Administration in 2017 found that patients perceive an unmet need for new treatments with less traumatic routes of administration.[25] Additional data show that, although patients currently receiving prophylaxis for HAE are generally satisfied with their medication, they and their caregivers would be interested in novel treatments with a less burdensome and more discreet method of administration.[14,24] Because of these difficulties, an effective targeted oral prophylactic therapy with a favorable benefit-to-risk profile is a useful treatment option that improves patient QoL by reducing the burden of treatment. The patient-reported outcome results of this study, notably the improvements in the AE-QoL total score and TSQM global satisfaction score, suggest that berotralstat improves QoL and patient satisfaction in patients with HAE who choose prophylactic therapy. Interestingly, although an improvement in QoL was observed, the improvement was not as robust as the reduction in attack rates. This may be related to the large placebo effect observed in the QoL assessments. The cause of the large placebo effect is not fully understood. Factors that may have contributed to the placebo effect include the frequent physician visits and other aspects of clinical trial participation, and the convenience of oral prophylactic therapy (berotralstat or placebo) compared with intravenous or subcutaneous prophylactic therapy. These factors would be expected to provide equivalent QoL improvements for all treatment arms.

The primary study limitation was the relatively small number of patients in each treatment group, particularly in the groups who transitioned from placebo to berotralstat. The small sample, observed placebo effect, and large variance in patient-reported outcome measures limited the ability to quantitate the effects of berotralstat on those outcomes.

In many patients with HAE, the disease is managed with lifelong prophylactic therapy. The evidence of effectiveness and safety through 48 weeks of drug administration in this study support berotralstat as a beneficial treatment option that should be considered in treatment decision making.

Berotralstat is an oral, once-daily prophylactic therapy that demonstrated a sustained and clinically significant reduction in HAE attack rates for 48 weeks in this study, with a favorable balance of efficacy and safety. Berotralstat provides a simple, once-daily, oral alternative to current injectable prophylactic therapies for patients with HAE.

## Acknowledgments

The authors thank the study patients, their families and caregivers, and the investigators and site staff who participated in the study. The authors acknowledge Professor Marco Cicardi, MD, (deceased) for his many contributions to HAE research and the design and execution of the APeX-2 study. Editorial assistance was provided by Medical Leverage, funded by Biocryst Pharmaceuticals, Inc. All authors participated in the writing, review, revision, and approval of the content of the manuscript for submission. Medical writing support was provided by Edward K. Baldwin, PhD.

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## ONLINE REPOSITORY

### Trial design and data collection

B. L. Zuraw, W. P. Sheridan, S. C. Murray, D. T. Johnston, E. Aygören-Pürsün, J. Bernstein, W. R. Lumry, T. Craig, and H. A. Iocca, participated in the design of the study, design of study instruments, and planning of statistical analyses. B. L. Zuraw, J. M. Best, B. Desai, H. A. Iocca, E. Nagy, S. C. Murray, and W. P. Sheridan were involved with formal data analysis, methodology, project administration, and supervision. S. C. Murray was the lead study statistician. D. T. Johnston, W. R. Lumry, E. Aygören-Pürsün, J. Bernstein, J. S. Jacobs, R. Gower, H. J. Wedner, T. Craig, and S. Kiani-Alikhan were study investigators participating in the conduct of the study, including the recruitment and follow-up of patients (Table E1). All authors participated in the review and revision of the manuscript and approved the final draft.

### Detailed inclusion/exclusion criteria

Subjects were required to meet all of the following criteria to be eligible for the study.

1. Males and nonpregnant, nonlactating females 18 years of age or older (main study) or 12 to 17 years of age (substudy).
2. Able to provide written, informed consent. Subjects who are aged 12 to 17 years of age at screening for the substudy must be able to read, understand, and willing to sign an assent form in addition to a caregiver providing informed consent.
3. Subject weight of 40 kg or greater.
4. A clinical diagnosis of hereditary angioedema (HAE) type 1 or 2, defined as having a C1 esterase inhibitor (C1-INH) functional level below 50% and a complement 4 (C4) level below the lower limit of the normal (LLN) reference range, as assessed during the screening period. In the absence of a low C4 value drawn during the intercritical period (ie, subject is not having an HAE attack), 1 of the following is acceptable to confirm the diagnosis of HAE: (a) a *SERPING-1* gene mutation known or likely to be associated with HAE type 1 or 2 assessed during the screening period; (b) a confirmed family history of C1-INH deficiency; (c) a C4 redrawn and retested during an attack in the screening period with the results below the LLN reference range.

For subjects with C1-INH function 50% or greater but less than the assay LLN, a *SERPING-1* gene mutation known or likely to be associated with HAE type 1 or 2, as assessed during the screening period OR a repeat C1-INH functional level less than 50% was considered acceptable for enrollment.

5. Access to and ability to use 1 or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE (icatibant, plasma-derived C1-INH, ecallantide, or recombinant C1-INH). Cinryze used for acute treatment of HAE attacks is an acceptable medication for this purpose.
6. Subjects must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study.
7. The subject must have at least 2 HAE attacks that meet all of the requirements that follow during the run-in period of a maximum of 56 days from the screening visit:
   - The attacks are unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack.
   - The attacks must either have been treated, have required medical attention, or be documented to cause functional impairment based on subject entry in the diary. Functional impairment is defined as the subject being unable to perform their daily activities without restriction (ie, subject records that they are at least slightly restricted in their daily activities during their HAE attack).
   - The attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling.
   - The attacks are confirmed by the investigator to be HAE attacks. Subjects will be contacted within 2 business days of the attack to discuss the attack, any queries on the entered data in the e-diary, as applicable.
   - Subjects who have recorded 2 such attacks may be randomized to the study drug beginning on or after day 28 of the run-in period; subjects who have recorded at least 3 such attacks may be randomized to the study drug beginning on or after day 14 of the run-in period. Under no circumstances should the run-in attack requirement for eligibility be disclosed to the study subjects.
8. Female subjects must meet at least 1 of the following requirements:
   - Be a woman of childbearing potential (defined as a nonmenopausal adult or adolescent female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure) who agrees to use at least an acceptable effective contraceptive method during the study and for a duration of 30 days after the last dose of the study drug.
   - Female subjects of childbearing potential who declare themselves as either sexually abstinent or exclusively having female sexual partners do not need to use an acceptable method of contraception. Abstinence in this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject."
   - Be a woman of non-childbearing potential (defined as postmenopausal for 2 or more years or having a follicle-stimulating hormone greater than 40 mIU/mL if postmenopausal 2 years or less or have had a hysterectomy, bilateral oophorectomy, or documented ovarian failure).
9. Male subjects must comply with the following requirements through the end of the study:
   - Subjects with female partners of childbearing potential (defined as postmenopausal 2 years or less or a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure) must agree to utilize at least 1 acceptably effective contraceptive method.
   - Male subjects who declare themselves as sexually abstinent are acceptable for the purposes of this study. Abstinence in this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject."
10. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. The subject must demonstrate adequate compliance with all study procedures required from the screening visit through randomization, including

diary recording of HAE attacks beginning at the screening visit.

### Exclusion criteria

Patients were excluded if any of the following conditions were present.

1. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject by participating in the study.
2. Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
3. Anticipated use of short-term prophylaxis of angioedema attacks for a preplanned procedure during the screening or study periods (parts 1 and 2 only).
4. Concurrent diagnosis of any other type of recurrent angioedema.
5. Clinically significant abnormal electrocardiogram at the screening visit. This includes, but is not limited to, a QT interval corrected by Fridericia formula (QTcF) greater than 470 ms for women, a QTcF greater than 450 ms for men, PR interval greater than 220 ms (both sexes), or ventricular and/or atrial premature contractions that are more frequent than occasional and/or as couplets or higher in grouping.
6. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.
7. Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
8. History of or current implanted defibrillator or pacemaker.
9. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the investigator, is clinically significant and relevant for this study. A calculated creatinine clearance of 30 mL/min or less or aspartate transaminase or alanine transaminase value 3 or more $\times$ the upper limit of the normal reference range value obtained during screening is exclusionary.
10. Prior enrollment in a berotralstat (BCX7353) study.
11. Suspected C1-INH resistance in the opinion of the investigator or sponsor.
12. History of alcohol or drug abuse within the previous year prior to the screening visit, or current evidence of substance dependence or abuse (self-reported alcoholic intake $>$ 3 drinks/d).
13. Positive serology for human immunodeficiency virus or current infection with hepatitis B virus or hepatitis C virus.
14. Pregnant, planning to become pregnant during the study, or nursing.
15. Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).
16. History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.
17. Use of androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to the screening visit or initiation during the study. Prophylaxis is defined as administration of a medication in the absence of symptoms of an HAE attack.
18. Use of C1-INH for prophylaxis of HAE attacks within the 14 days prior to the screening visit or initiation during the study. Use of a C1-INH therapy for treatment of attacks is not excluded at any time, nor is C1-INH for preprocedure prophylaxis for an unplanned/unforeseen procedure. Prophylaxis is defined as administration of a medication in the absence of symptoms of an HAE attack.
19. Use of concomitant medications that are metabolized by cytochrome P450 (CYP) 2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.
20. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study.
21. Use of a medication that is transported by p-glycoprotein efflux pump and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.
22. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
23. Initiation of an estrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study (parts 1 and 2 only). Established use (initiation $\geq$ 56 days prior to screening) during the study is permitted.
24. Current participation in any other investigational drug study or received another investigational drug within 30 days of the screening visit.
25. An immediate family relationship to either sponsor employees, the investigator, or employees of the study site named on the delegation log.
26. Held in an institution by a government or judicial order.

## Safety data

### Definitions for the adverse events tables

Adverse events (AEs) are coded using the Medical Dictionary for Regulatory Activities (MedDRA) v19.1.

Treatment-emergent adverse events (TEAEs) are defined as those events that occur after initiation of the study drug through week 48 or the last dose of study drug plus 30 days if the patient discontinued prior to week 48.

A drug-related TEAE is defined as any AE in which the investigator defines the relationship as possibly related, probably related, or definitely related.

### Effectiveness outcomes

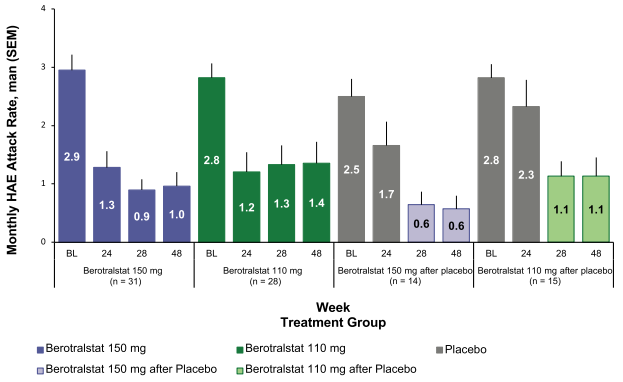


**FIGURE E1.** Mean (standard error of the mean [SEM]) investigator-confirmed attack rate at baseline (BL), 24 weeks, 28 weeks, and 48 weeks by treatment arm in patients who completed dosing to week 48. Error bars represent the SEM. Attack rates are for the 4 weeks preceding each visit.

## Patient-reported outcomes

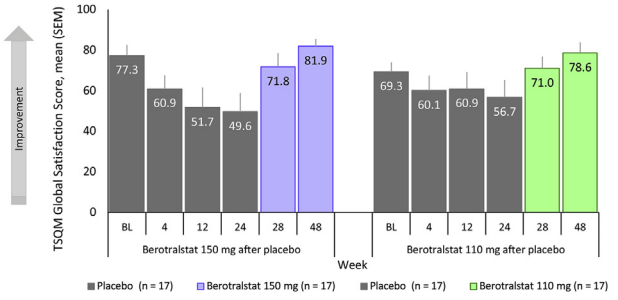


**FIGURE E2.** Mean (SEM) Treatment Satisfaction Questionnaire for Medication (TSQM) global satisfaction scores by visit week among patients rerandomized from placebo to berotralstat. An increase indicates greater satisfaction. Error bars represent the SEM.

**TABLE E1.** List of study investigators and locations

| Investigator name | Location |
|---|---|
| United States | |
| Anderson, John | Birmingham, AL |
| Banerji, Aleena | Boston, MA |
| Bernstein, Jonathan | Cincinnati, OH |
| Busse, Paula | New York, NY |
| Craig, Timothy | Hershey, PA |
| Diaz, Joseph | San Antonio, TX |
| Fritz, Stephen | Clackamas, OR |
| Gower, Richard | Spokane, WA |
| Jacobs, Joshua | Walnut Creek, CA |
| Johnston, Douglas T. | Charlotte, NC |
| Li, H. Henry | Chevy Chase, MD |
| Lumry, William T. | Dallas, TX |
| McNeil, Donald | Columbus, OH |
| Mumneh, Nayla | Piscataway, NJ |
| Otto, William | Austin, TX |
| Riedl, Marc | San Diego, CA |
| Shapiro, Ralph | Plymouth, MN |
| Sitz, Karl | Little Rock, AR |
| Soteres, Daniel | Colorado Springs, CO |
| Tachdjian, Raffi | Santa Monica, CA |
| Wedner, H. James | St. Louis, MO |
| Canada | |
| Gagnon, Remi | Quebec, Quebec |
| Sussman, Gordon | Toronto, Ontario |
| Yang, William | Ottawa, Ontario |
| Europe | |
| Aygören-Pürsün, Emel | Frankfurt, Germany |
| Bara, Noemi | Jud Mures, Romania |
| Bethune, Claire | Plymouth, UK |
| Bouillet, Laurence | Grenoble, France |
| Caballero, Teresa | Madrid, Spain |
| Fain, Olivier | Paris, France |
| Farkas, Henriette | Budapest, Hungary |
| Grivcheva-Panovska, Vesna | Skopje, Macedonia |
| Hakl, Roman | Brno, Czech Republic |
| Hanzlíková, Jana | Plzen, Czech Republic |
| Kiani-Alikhan, Sorena | London, UK |
| Kinaciyan, Tamar | Vienna, Austria |
| Manson, Ania | Cambridge, UK |
| Maurer, Marcus | Berlin, Germany |
| Tejerina, Teresa Gonzalez-Quevedo | Madrid, Spain |
| Yong, Patrick | Camberley, UK |

**TABLE E2.** TEAEs (medical concepts) occurring in ≥ 10% of patients in any berotralstat group

| | Up to 48 weeks exposure | | Up to 24 weeks exposure | | |
|---|---|---|---|---|---|
| Medical concept | 150 mg (n = 40) n (%) | 110 mg (n = 41) n (%) | 150 mg after placebo (n = 17) n (%) | 110 mg after placebo (n = 17) n (%) | Placebo (n = 39) n (%) |
| Upper respiratory tract infection* | 21 (52.5) | 15 (36.6) | 3 (17.6) | 4 (23.5) | 11 (28.2) |
| Nausea | 8 (20.0) | 8 (19.5) | 3 (17.6) | 1 (5.9) | 7 (17.9) |
| Abdominal pain* | 12 (30.0) | 4 (9.8) | 2 (11.8) | 2 (11.8) | 4 (10.3) |
| Dyspepsia | 5 (12.5) | 4 (9.8) | 2 (11.8) | 1 (5.9) | 3 (7.7) |
| Diarrhea* | 7 (17.5) | 5 (12.2) | 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Vomiting | 6 (15.0) | 4 (9.8) | 2 (11.8) | 0 (0.0) | 1 (2.6) |
| Headache | 5 (12.5) | 4 (9.8) | 0 (0.0) | 0 (0.0) | 2 (5.1) |
| Flatulence | 3 (7.5) | 3 (7.3) | 2 (11.8) | 0 (0.0) | 1 (2.6) |
| Back pain | 5 (12.5) | 2 (4.9) | 0 (0.0) | 0 (0.0) | 1 (2.6) |
| Gastroesophageal reflux disease | 2 (5.0) | 4 (9.8) | 2 (11.8) | 0 (0.0) | 0 (0.0) |

*The terms Upper respiratory tract infection, Abdominal pain, and Diarrhea are medical concepts that contain multiple preferred terms. Upper respiratory tract infection contains the preferred terms Nasopharyngitis, Upper respiratory tract infection, and Viral upper respiratory tract infection. Abdominal pain contains the preferred terms Abdominal pain, Abdominal discomfort, Abdominal pain upper, and Abdominal tenderness. Diarrhea contains the preferred terms Diarrhea and Frequent bowel movements.

**TABLE E3.** Grade 3 or 4 TEAEs through week 48, safety population

| | Up to 48 weeks exposure | | Up to 24 weeks exposure | | |
|---|---|---|---|---|---|
| AE | 150 mg (n = 40) n (%) | 110 mg (n = 41) n (%) | 150 mg after placebo (n = 17) n (%) | 110 mg after placebo (n = 17) n (%) | Placebo (n = 39) n (%) |
| Any grade 3 or 4 AE | 3 (7.5) | 5 (12.2) | 1 (5.9) | 1 (5.9) | 3 (7.7) |
| GI disorders | 1 (2.5)<br>1 patient with 2 episodes of anal incontinence | 3 (7.3)<br>2 patients abdominal pain, 1 patient with 2 episodes of toothache | – | 1 (5.9)<br>Large intestine polyp | 1 (2.6)<br>Diverticulum intestinal hemorrhagic*† |
| Infections and infestations | – | 1 (2.4)<br>Oral herpes | – | – | 1 (2.6)<br>Pneumonia |
| Neoplasms | – | 1 (2.4)<br>Plasma cell myeloma* | 1 (5.9)<br>Uterine leiomyoma* | – | – |
| General disorders and administration site conditions | 1 (2.5)<br>Chest pain | – | – | – | – |
| Investigations | 1 (2.5)<br>Medical observation*‡ | – | – | – | 1 (2.6)<br>GGT increased |
| Musculoskeletal and connective tissue disorders | 1 (2.5)<br>Back pain | – | – | – | – |
| Nervous system disorders | – | – | – | – | 1 (2.6)<br>Transient ischemic attack*† |
| Skin and subcutaneous tissue disorders | – | 1 (2.4)<br>Purpura | – | – | – |

*GGT*, Gamma-glutamyltransferase; *GI*, gastrointestinal.
*Serious adverse event (SAE).
†Diverticulum intestinal hemorrhagic and transient ischemic attack occurred in the same patient.
‡This medical observation was the only SAE reported during part 2. Per the local standard of care, the patient was hospitalized for a routine screening procedure.