Original Article

Once-Daily Oral Berotralstat for Long-Term Prophylaxis of Hereditary Angioedema: The Open-Label Extension of the APeX-2 Randomized Trial

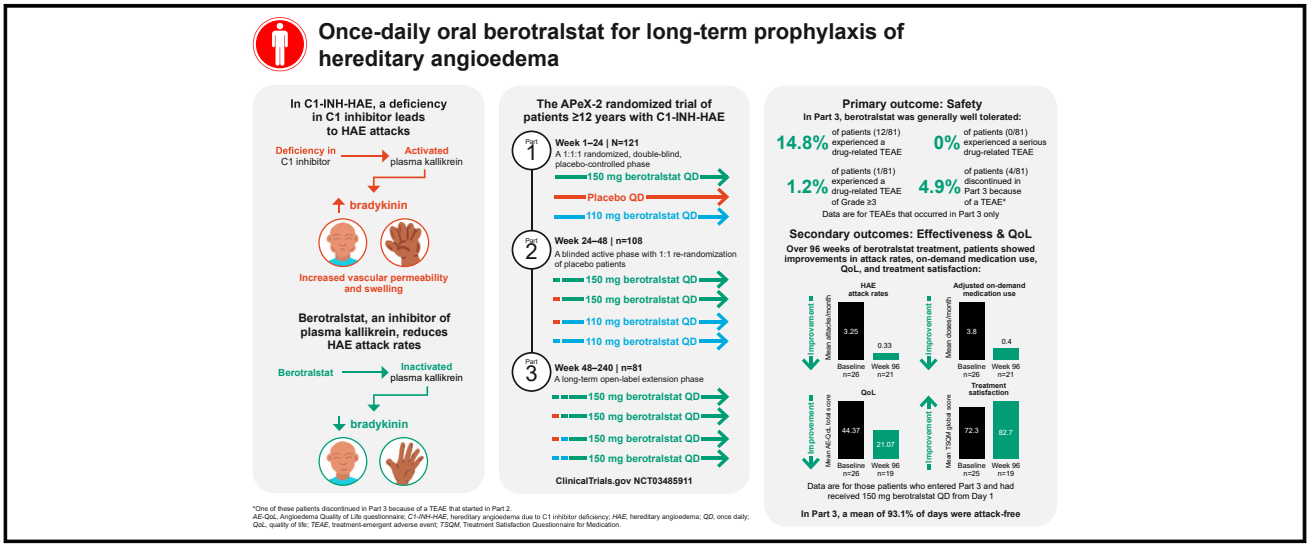
Sorena Kiani-Alikhan, MBPhD[a], Richard Gower, MD[b], Timothy Craig, DO[c], H. James Wedner, MD[d], Tamar Kinaciyan, MD[e], Emel Aygören-Pürsün, MD[f], Aleena Banerji, MD[g], Jonathan A. Bernstein, MD[h], John Anderson, MD[i], Phil Collis, PhD[j], Douglas T. Johnston, DO[j], Bhavisha Desai, PharmD[j,*], Dianne Tomita, MPH[j], Rémi Gagnon, MD[k], Raffi Tachdjian, MD[l], Daniel F. Soteres, MD[m], Henriette Farkas, MD, PhD, DSc[n], Teresa Caballero, MD, PhD[o], Donald McNeil, MD[p], Joshua Jacobs, MD[q], and William R. Lumry, MD[r]; on behalf of the APeX-2 investigators *London, United Kingdom; Spokane, Wash; Hershey, Pa; St. Louis, Mo; Vienna, Austria; Frankfurt, Germany; Boston, Mass; Cincinnati and Columbus, Ohio; Birmingham, Ala; Durham, NC; Québec, QC, Canada; Los Angeles and Walnut Creek, Calif; Colorado Springs, Colo; Budapest, Hungary; Madrid, Spain; and Dallas, Texas*

What is already known about this topic? Berotralstat, which is approved for the prophylaxis of hereditary angioedema attacks in patients 12 years or older, was shown to be well tolerated and effective over 48 weeks in parts 1 and 2 of the APeX-2 randomized phase 3 study.

What does this article add to our knowledge? In APeX-2 part 3, once-daily oral berotralstat for prophylaxis of hereditary angioedema attacks was well tolerated long term and led to sustained improvements in attack rates and patient-reported outcomes over 96 weeks of treatment.

How does this study impact current management guidelines? Long-term prophylaxis with once-daily oral berotralstat is an effective and well-tolerated nonparenteral treatment option for patients living with hereditary angioedema.

VISUAL SUMMARY



[a]Department of Immunology, Royal Free London NHS Foundation Trust, London, United Kingdom
[b]Marycliff Clinical Research, Spokane, Wash
[c]Department of Medicine and Pediatrics, Penn State University, Hershey Medical Center, Hershey, Pa
[d]Division of Allergy and Immunology, John T. Milliken Department of Medicine, Washington University School of Medicine, St. Louis, Mo
[e]Department of Dermatology, Medical University of Vienna, Vienna, Austria
[f]Department for Children and Adolescents, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany

Abbreviations used

AE-QoL- Angioedema Quality of Life questionnaire
C1-INH- C1 inhibitor
C1-INH-HAE- Hereditary angioedema due to C1 inhibitor deficiency
C4- Complement 4
EAACI- European Academy of Allergy and Clinical Immunology
HAE- Hereditary angioedema
LLN- Lower limit of normal
MCID- Minimal clinically important difference
QD- Once daily
QoL- Quality of life
SEM- Standard error of the mean
TEAE- Treatment-emergent adverse event
TESAE- Treatment-emergent serious adverse event
TSQM- Treatment Satisfaction Questionnaire for Medication
WAO- World Allergy Organization

BACKGROUND: Berotralstat is a first-line, once-daily oral plasma kallikrein inhibitor approved for prophylaxis of hereditary angioedema (HAE) attacks in patients 12 years or older.
OBJECTIVE: This analysis examined the safety and effectiveness of long-term prophylaxis with berotralstat.
METHODS: APeX-2 was a phase 3, parallel-group, multicenter trial in patients with HAE caused by C1-inhibitor deficiency (NCT03485911). Part 1 was a randomized, double-blind, placebo-controlled evaluation of 150 and 110 mg of berotralstat over 24 weeks. In part 2, berotralstat-treated patients continued the same treatment, and placebo-treated patients were re-randomized to 150 or 110 mg of berotralstat for 24 weeks. In part 3, all patients were treated with open-label berotralstat at 150 mg, which could be continued for up to an additional 4 years. In part 3, the primary endpoint was long-term safety and tolerability. Secondary endpoints included HAE attack rates and quality of life (QoL).
RESULTS: Eighty-one patients entered part 3. Treatment-emergent adverse events (TEAEs) occurred in 82.7% of patients, with most being mild or moderate in severity. The most common TEAEs were nasopharyngitis, urinary tract infection, abdominal pain, arthralgia, coronavirus infection, and diarrhea. Drug-related TEAEs occurred in 14.8% of patients, but none were serious. For patients who completed 96 weeks of berotralstat treatment (n = 70), the mean (standard error) change in attack rate from baseline was −2.21 (0.20) attacks/mo. Clinically meaningful improvements in QoL were also observed, with the largest improvements in the *functioning* domain.
CONCLUSION: Berotralstat was generally well tolerated, provided rapid and sustained reductions in HAE attacks and improved QoL over 96 weeks. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Angioedema; Hereditary; Complement C1 inhibitor protein; Berotralstat; Plasma kallikrein inhibitor; Prophylaxis; Oral therapy*

Hereditary angioedema (HAE) is a rare disease that can be classified as C1 inhibitor (C1-INH)−deficient HAE (C1-INH-HAE) or C1-INH−normal HAE.[1,2] C1-INH-HAE, with an estimated prevalence of around 1 in 50,000 individuals,[2] is

[g]Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Mass
[h]Division of Immunology, Rheumatology, and Allergy, Department of Medicine, University of Cincinnati and Bernstein Clinical Research Center, Cincinnati, Ohio
[i]Clinical Research Center of Alabama, an affiliate of AllerVie Health, Birmingham, Ala
[j]BioCryst Pharmaceuticals, Inc., Durham, NC
[k]Clinique Spécialisée en Allergie de la Capitale, Québec, QC, Canada
[l]Department of Pediatrics, University of California, Los Angeles, Los Angeles, Calif
[m]Asthma & Allergy Associates, Colorado Springs, Colo
[n]Hungarian Angioedema Center of Reference and Excellence, Department of Internal Medicine and Haematology, Semmelweis University, Budapest, Hungary
[o]Allergy Department, La Paz University Hospital, IdiPAZ Group 44, CSUR Angioedema Hereditario HULP, Madrid, Spain
[p]Optimed Research, Ltd., Columbus, Ohio
[q]Allergy & Asthma Clinical Research, Walnut Creek, Calif
[r]AARA Research Center, Dallas, Texas
*Former employee of BioCryst Pharmaceuticals, Inc.

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Conflicts of interest: J. Anderson is on the advisory boards for BioCryst Pharmaceuticals, BioMarin Pharmaceutical, CSL Behring, Cycle Pharmaceuticals, Pharming, and Takeda; clinical trial investigator for BioCryst Pharmaceuticals, BioMarin Pharmaceutical, CSL Behring, KalVista Pharmaceuticals, Pharming, Pharvaris, and Takeda; and speakers bureau for BioCryst Pharmaceuticals, CSL Behring, Pharming, and Takeda. E. Aygören-Pürsün is on the advisory boards for BioMarin Pharmaceutical, Centogene, CSL Behring, KalVista Pharmaceuticals, Pharming, Pharvaris, and Takeda; received consultancy fees from BioCryst Pharmaceuticals, KalVista Pharmaceuticals, and Pharvaris; received grants from CSL Behring and Takeda; is the speaker for BioCryst Pharmaceuticals, Centogene, CSL Behring, Pharming and Takeda; and received travel support from CSL Behring and Takeda. A. Banerji is on the advisory boards for BioCryst Pharmaceuticals, BioMarin Pharmaceutical, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharvaris, and Takeda; and received grants from BioCryst Pharmaceuticals, Ionis Pharmaceuticals, KalVista Pharmaceuticals, and Takeda. J. A. Bernstein is on the advisory boards for, and received consultancy fees and grants from, BioCryst Pharmaceuticals, BioMarin Pharmaceutical, CSL Behring, KalVista Pharmaceuticals, Ionis Pharmaceuticals, Pharming, and Takeda; has a role in Allergists for Israel (Chair), American Academy of Allergy, Asthma & Immunology (President Elect), Angioedema Centers of Reference and Excellence/Urticaria Centers of Reference and Excellence (joint task force), Interasma (board of directors), and World Allergy Organization (board of directors); and is the speaker for Astria Therapeutics, BioCryst Pharmaceuticals, BioMarin Pharmaceutical, CSL Behring, Escient Pharmaceuticals, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Ono Pharmaceutical, Pharming, and Takeda. P. Collis and B. Desai are employees of and own stock in BioCryst Pharmaceuticals. T. Caballero is on the advisory boards for Astria Therapeutics, BioCryst Pharmaceuticals, CSL Behring, Novartis, Pharming, and Takeda; clinical trial or registry investigator for BioCryst Pharmaceuticals, CSL Behring, Ionis Pharmaceuticals, Novartis, Pharming, and Takeda; received consultancy fees from Astria Therapeutics, BioCryst Pharmaceuticals, CSL Behring, Novartis, Pharming, and Takeda; grants from CSL Behring and Takeda; patient medication from BioCryst Pharmaceuticals and Novartis; and royalties from CSL Behring, Ionis Pharmaceuticals, and Takeda; is the speaker for BioCryst Pharmaceuticals, CSL Behring, Novartis, Pharming, and Takeda; and received travel support from BioCryst Pharmaceuticals, CSL Behring, Novartis, Pharming, and Takeda. T. Craig received consultancy fees from BioCryst Pharmaceuticals, BioMarin Pharmaceutical, CSL Behring, Ionis Pharmaceuticals, Spark Therapeutics, and Takeda; research grants from BioMarin Pharmaceutical, CSL Behring, Intellia Therapeutics, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharvaris, and Takeda; and is the speaker for BioCryst Pharmaceuticals, CSL Behring, and Takeda. H. Farkas is on the advisory boards for Astria Therapeutics, BioCryst Pharmaceuticals, CSL Behring, KalVista Pharmaceuticals, Ono Pharmaceutical, Pharming, Pharvaris, and Takeda; received grants from, and is the speaker for, CSL Behring, Pharming, and Takeda; and travel support from CSL Behring, KalVista Pharmaceuticals, Pharming, and Takeda. R. Gagnon is on the advisory boards for ALK, AstraZeneca, Bausch +

caused by diverse mutations in the C1-INH—encoding gene *SERPING1*.[3] Whereas mutations in type 1 C1-INH-HAE lead to reduced levels of C1-INH, mutations in type 2 C1-INH-HAE lead to the production of dysfunctional C1-INH.[4] In both types, a deficiency of C1-INH activity prevents inactivation of plasma kallikrein. This results in the unregulated production of bradykinin and transient increases in vascular permeability and angioedema.[5]

Localized, subcutaneous, and/or submucosal swelling is a classic sign of C1-INH-HAE and most commonly affects the extremities, face, abdomen, and larynx.[6,7] These swelling attacks are recurrent and lead to significant morbidity; they can be associated with pain, discomfort, dysfunction, disfigurement, and/or other symptoms depending on the individual and affected organ.[8] Attacks can be life-threatening if the airway is affected because of the risk of asphyxiation.[8] Furthermore, because attacks are unpredictable in nature, they place a considerable physical, social, and psychological burden on patients.[9]

Management of HAE aims to stop attacks or reduce their frequency, severity, and duration,[10] and includes on-demand treatment administered at swelling onset, short-term prophylaxis before known attack triggers, and long-term prophylaxis.[2,11] The 2021 World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guidelines for HAE recommend that all patients be considered for long-term prophylaxis.[12] Current targeted treatment options include C1-INH replacement, kallikrein inhibition, and bradykinin B2 receptor inhibition.[13] These treatments have expanded the HAE armamentarium and are better tolerated than some older treatments, such as attenuated androgens. However, most are injectable medicines requiring either intravenous or subcutaneous administration,[14,15] which can be burdensome.[11,16,17]

Berotralstat (BCX7353), which has been approved in the United States, several European countries, Japan, and other countries in the rest of the world for prophylaxis of HAE attacks in patients 12 years or older, is an oral, once-daily (QD), highly selective inhibitor of plasma kallikrein.[18-20] The 150 mg dose is available in all countries where berotralstat is approved and is the recommended dose of berotralstat.[19,21] Berotralstat 110 mg is also approved in the United States; however, the dose reduction to 110 mg is reserved for use in certain populations, including patients with moderate or severe hepatic impairment and patients who experience persistent gastrointestinal reactions while on the 150 mg dose.[21] The WAO/EAACI guidelines recommend the use of berotralstat as a first-line long-term prophylactic treatment option.[12]

The pivotal study that led to approval of berotralstat was APeX-2 (NCT03485911), a phase 3 clinical trial conducted in patients with C1-INH-HAE. In part 1, berotralstat significantly reduced the rate of HAE attacks compared with placebo during the 24-week treatment period (2.35 attacks/mo in the placebo group vs 1.31 [$P < .001$] and 1.65 [$P = .024$] attacks/mo in patients treated with 150 and 110 mg of berotralstat QD, respectively).[22] HAE attack rates continued to decline in part 2.[18] By week 48, the mean attack rates were 1.06 and 1.35 attacks/mo for patients who had received 150 and 110 mg of berotralstat QD for 48 weeks, respectively. Berotralstat was generally well tolerated throughout the 48 weeks, with most treatment-emergent adverse events (TEAEs) being mild or moderate and no serious drug-related TEAEs reported.[18] Here,

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Corresponding author: William R. Lumry, MD, AARA Research Center, 10100 N. Central Expressway, Ste 100, Dallas, TX 75231. E-mail: lumrymd@aararesearch.com.

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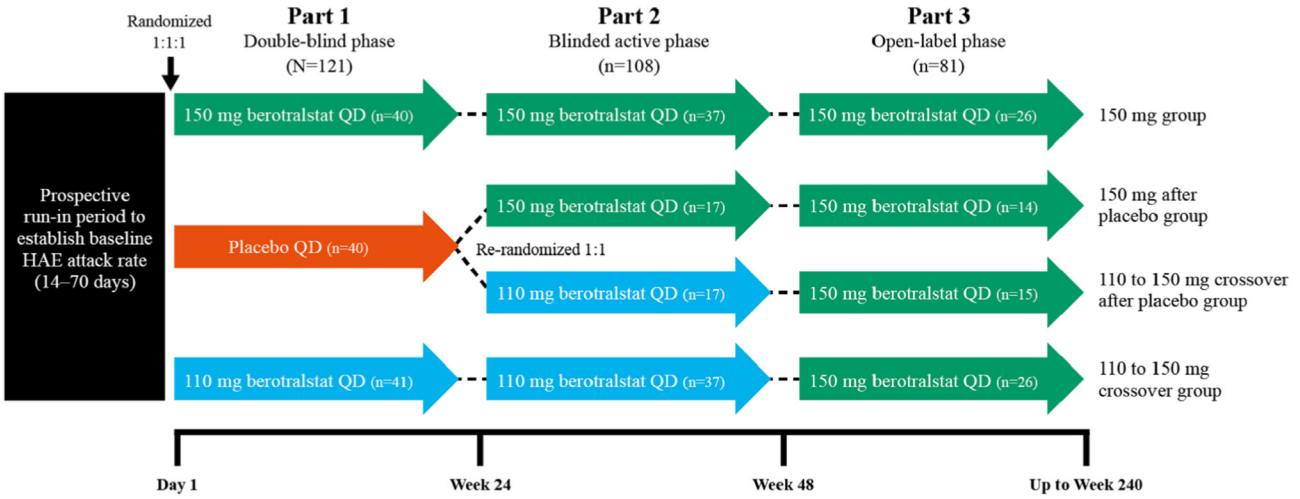

FIGURE 1. APeX-2 phase 3 study design. *HAE*, Hereditary angioedema; *QD*, once daily.

we report long-term safety, effectiveness, and quality of life (QoL) data of patients who continued into part 3 of APeX-2.

METHODS

Study design

APeX-2 was a parallel-group, multicenter, phase 3 clinical trial comprising 3 parts (Figure 1). Part 1 was a 1:1:1 randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of 150 and 110 mg of berotralstat QD versus placebo over 24 weeks.[22] In part 2, which primarily evaluated safety and tolerability, patients who were being treated with berotralstat continued the same blinded daily dose for an additional 24 weeks, and patients who were being treated with placebo in part 1 were re-randomized 1:1 to receive either 150 or 110 mg of berotralstat QD for the next 24 weeks.[18]

At week 48, patients had to reconsent to continue into part 3, a long-term, open-label extension that was added as an amendment to the original protocol to allow further data collection up to 240 weeks. Based on the results of the part 1 analysis, which demonstrated greater efficacy and no increase in safety or tolerability risk at the 150 mg dose compared with the 110 mg dose, all patients crossed over to or continued 150 mg of berotralstat QD in part 3. Safety, tolerability, effectiveness, and QoL were evaluated.

The study protocol and other documentation were submitted to and approved by relevant regulatory authorities and institutional review boards/independent ethics committees. The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation and Good Clinical Practice guidelines. An independent data monitoring committee reviewed safety data at prespecified intervals, with additional consultation or review as needed.

Patients

Patients were eligible for participation in the study if they had a clinical diagnosis of type 1 or 2 HAE and were 12 years or older at study sites in North America or 18 years or older at study sites in Europe. Type 1 or 2 HAE was defined as having a C1-INH functional level <50% and a complement 4 (C4) level below the lower limit of normal (LLN). Patients also had to have had ≥2 HAE attacks in the prospective run-in period and access to ≥1 approved on-demand treatment. Patients with a C1-INH functional level between 50% and 74% or a C4 level above the LLN could also enroll in the study based on alternative protocol-specified criteria, which included having a *SERPING1* gene mutation known or likely to be associated with type 1 or 2 HAE (available in this article's Online Repository at www.jaci-inpractice.org).

Patients were excluded if they were on prophylactic treatment for HAE and/or had previously been enrolled in another berotralstat study. A full list of exclusion criteria is in this article's Online Repository at www.jaci-inpractice.org.

Overall, patients were recruited at 40 sites across 11 countries (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).[18] All patients or their caregivers provided written informed consent or assent before study initiation. Patients who completed treatment with berotralstat in part 2 were eligible to continue into part 3 but had to reconsent.

Treatment interventions

Treatment interventions for parts 1 and 2 have been previously described.[18,22] In part 3, treatment was administered in an open-label manner. Patients who had been on 150 mg of berotralstat QD in part 2 continued the same dosage in part 3, and patients who had been on 110 mg of berotralstat QD in part 2 crossed over to 150 mg of berotralstat QD in part 3.

Outcomes

The primary objective of part 3 was to evaluate the long-term safety and tolerability of oral berotralstat QD from week 48. The primary endpoints were the number and proportion of patients who experienced a TEAE, a treatment-emergent serious adverse event (TESAE), a grade 3 or 4 TEAE, a grade 3 or 4 laboratory abnormality, a TEAE consistent with drug rash, and discontinuation because of a TEAE.

Secondary endpoints included the number and rate of HAE attacks, durability of response (ie, attack rate trend over time), the number and proportion of days with HAE symptoms, use of HAE attack medications, and durability in QoL scores, as measured using questionnaires such as the Angioedema Quality of Life questionnaire (AE-QoL) and the Treatment Satisfaction Questionnaire for Medication (TSQM). For the AE-QoL, a decrease in the score (score

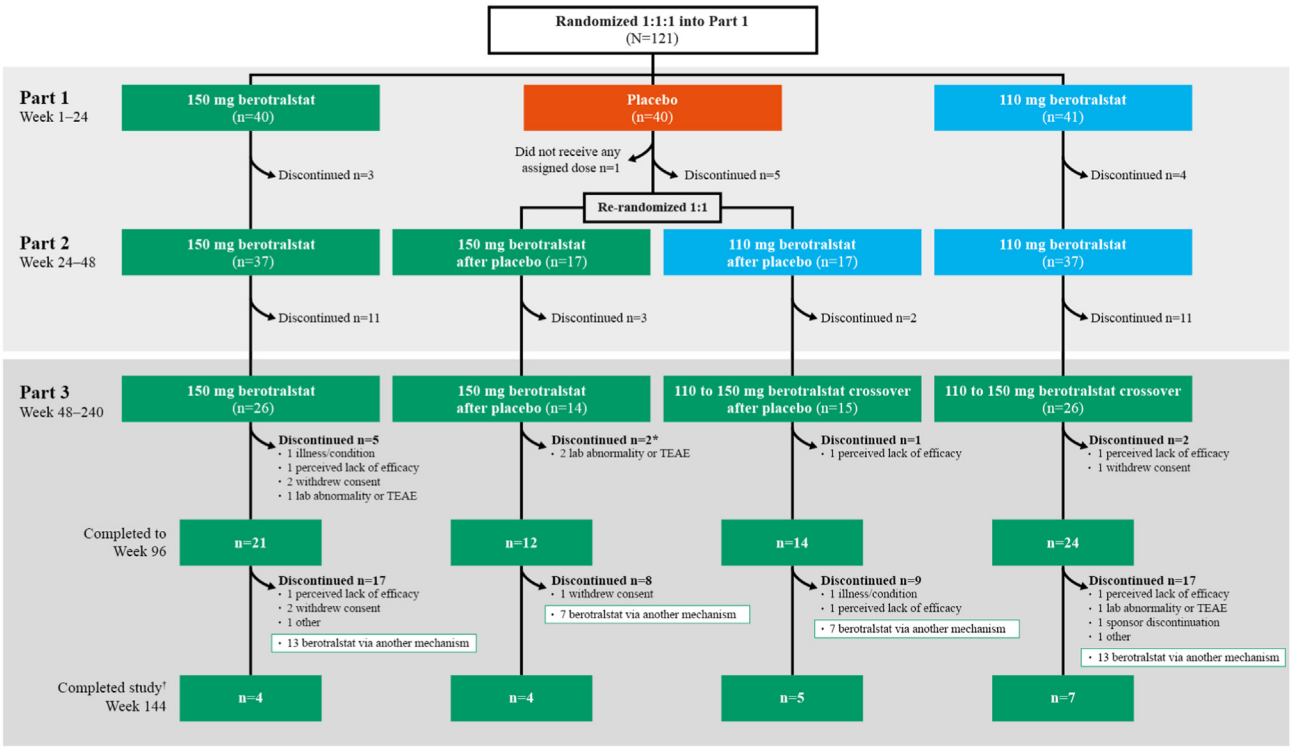

FIGURE 2. Patient disposition in APeX-2. Reasons for discontinuation are shown for patients who entered part 3. Information about discontinuations that occurred in parts 1 and 2 can be found in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org) and in the respective publications.[18,22] Patients who went on to receive berotralstat off-study via another mechanism (ie, switched to commercial berotralstat) were considered to have discontinued. *One patient in the 150 mg after placebo group discontinued treatment in part 3 (day 494) because of a TEAE that started in part 2 (day 184). †Patients who enrolled under the original protocol were considered to have completed the study on reaching week 144. However, some patients (n = 20) reached or continued past week 144 but were not considered to have completed the study because they enrolled after a protocol amendment extended the study to up to 240 weeks. *TEAE*, treatment-emergent adverse event.

range: 0-100) indicates an improvement in QoL, and a change of 6 points in the total score is defined as the minimal clinically important difference (MCID).[23] For the TSQM, an increase in the score (score range: 0-100) indicates greater satisfaction.[24]

Information regarding assessments and reporting of attacks can be found in this article's Online Repository at www.jaci-inpractice.org.

Statistical analyses

Analyses are for all patients who received at least 1 dose of berotralstat in part 3 and are summarized by the treatment group (defined based on the type and dose of treatment received across the entire study; Figure 1).

HAE attack rates, on-demand medication use, and patient-reported outcomes are shown through 96 weeks of active berotralstat treatment because past this point, many patients discontinued the study to receive commercially available berotralstat. Data are only shown for selected months. A month is defined as 28 days.

The number and percentage of HAE attack–free days are shown for part 3 only. Duration of attack-free periods is reported for the entire study.

HAE attacks are based on adjusted subject-reported attacks (available in this article's Online Repository at www.jaci-inpractice.org). Adjusted subject-reported attack rates were defined as the total number of adjusted subject-reported HAE attacks experienced in a period, adjusted for the length of a month (defined as 28 days) and the number of days during that period. Baseline rates are based on the run-in period.

Attack-free days were calculated by subtracting the number of days with angioedema symptoms from the duration of the reporting period of interest for each patient.

Baseline rates for on-demand medication use are calculated similarly to attack rates and are based on the run-in period.

Baseline values for patient-reported outcomes are based on day 1 assessments before study drug administration. The reference values for the 2 placebo groups are values at berotralstat initiation after 6 months on placebo.

Categorical measurements are summarized using frequencies and percentages, and continuous measurements are summarized descriptively using mean (standard error of the mean [SEM]) or median (range) values, including mean change from baseline to (nominal) 96 weeks of berotralstat treatment.

Wilcoxon signed-rank *P* values are presented for patient-reported outcomes but are only nominal and should be considered a descriptive statistic.

Individual participant data beyond what has been presented in this paper will not be made available.

TABLE I. Demographics of the patients who entered part 3 of APeX-2

Demographic	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	All patients
N	26	14	15	26	81
Age (y)					
Mean (SD)	39.5 (14.5)	46.1 (14.9)	45.1 (15.9)	41.0 (18.7)	42.1 (16.2)
Range	12-60	14-68	17-72	12-72	12-72
Age groups (y), n (%)					
≤17	2 (7.7)	1 (7.1)	1 (6.7)	2 (7.7)	6 (7.4)
≥65	0	2 (14.3)	1 (6.7)	4 (15.4)	7 (8.6)
Female sex*, n (%)	16 (61.5)	10 (71.4)	10 (66.7)	19 (73.1)	55 (67.9)
Race*, n (%)					
Black or African American	1 (3.8)	1 (7.1)	0	0	2 (2.5)
White	24 (92.3)	12 (85.7)	15 (100)	26 (100)	77 (95.1)
Other	1 (3.8)	1 (7.1)	0	0	2 (2.5)
Weight at screening (kg), mean (SD)	87.9 (19.6)	87.7 (22.7)	84.0 (24.2)	79.1 (20.7)	84.3 (21.3)
BMI at screening (kg/m^2), mean (SD)	30.0 (6.0)	30.3 (7.7)	29.3 (7.2)	27.9 (7.2)	29.3 (6.9)
Baseline attack rate† (attacks/mo), mean (SD)	3.3 (2.02)	2.7 (1.63)	3.0 (0.84)	3.2 (1.93)	3.1 (1.74)

BMI, Body mass index; *SD*, standard deviation.
*Information regarding sex and race was captured at the screening visit. Race was self-reported.
†Baseline attack rates are adjusted subject-reported attack rates.

RESULTS

Patients

A total of 81 patients completed part 2 and received at least 1 dose of berotralstat in part 3 (Figure 2). The demographic characteristics of these patients were generally similar across all treatment groups (Table I).

Most discontinuations in part 3 occurred after week 96, with 10 patients (12.3%) discontinuing treatment in part 3 before this point (Figure 2). Of the 51 discontinuations that occurred after week 96, 78.4% (40 of 51) were attributed to patients receiving berotralstat via another mechanism and were not related to TEAEs or lack of efficacy. Discontinuations occurring in parts 1 and 2 are listed in Table E2, available in this article's Online Repository at www.jaci-inpractice.org.

Safety

The overall summary of TEAEs experienced by the 81 patients who entered part 3 is shown in Table II. As a detailed description of TEAEs in parts 1 and 2 is already published,[18] here we focus on the TEAEs that occurred in part 3.

In part 3, all 81 patients were treated with 150 mg of berotralstat and were treated for a median (range) of 644 (22-981) days. During this time, 67 of the 81 patients (82.7%) experienced at least 1 TEAE, with the rate being similar across treatment groups. The most common TEAEs (≥5%) were nasopharyngitis (19.8%), urinary tract infection (9.9%), abdominal pain (6.2%), arthralgia (6.2%), coronavirus infection (6.2%), and diarrhea (6.2%) (Table III). A total of 12 patients (14.8%) experienced at least 1 drug-related TEAE, with most drug-related events belonging to the *Gastrointestinal disorders* System Organ Class (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Drug-related TEAEs occurred in a similar percentage of patients across all treatment groups (13.3%-15.4%), and no patients experienced drug-related rash.

In part 3, a total of 18 patients (22.2%) experienced abdominal-related gastrointestinal TEAEs, with the percentage being higher in patients who had previously been treated with placebo. This type of TEAE led to discontinuation of berotralstat in 2 cases. Four patients (4.9%) experienced drug-related abdominal-related gastrointestinal TEAEs.

Most TEAEs were mild or moderate in severity, with 10 patients (12.3%) experiencing a grade 3 or 4 TEAE in part 3. One of these was deemed to be drug-related: grade 3 abdominal pain in a patient from the 150 mg group. All grade 3 and 4 TEAEs are detailed in Table E4, available in this article's Online Repository at www.jaci-inpractice.org.

A total of 10 TESAEs occurred in 7 patients (8.6%) during part 3, but none were deemed drug related. These TESAEs were vascular stent occlusion and 2 events of acute myocardial infarction in the 150 mg group (n = 1); pyelonephritis and syncope in the 150 mg after placebo group (n = 2); pneumonia, bipolar disorder, and pleural effusion in the 110 to 150 mg crossover after placebo group (n = 2); and alcoholic gastritis and increase in obesity in the 110 to 150 mg crossover group (n = 2).

Grade 3 or 4 laboratory abnormalities occurred in all treatment groups (Table E5, available in this article's Online Repository at www.jaci-inpractice.org), but none were considered drug related. Grade 3 laboratory abnormalities occurred in 7 patients (8.6%) and included elevated glucose, elevated leukocyte count, abnormal prothrombin ratio, and abnormal activated partial thromboplastin time. One grade 4 laboratory abnormality, an abnormal activated partial thromboplastin time, was reported in 1 patient (1.2%). These laboratory abnormalities were transient.

Three patients (3.7%) discontinued berotralstat treatment in part 3 because of TEAEs that started in part 3: one patient in the 150 mg group at week 70 because of grade 3 abdominal pain, one patient in the 150 mg after placebo group at week 55 because of grade 2 abdominal pain and grade 2 diarrhea, and one patient in the 110 to 150 mg crossover group at week 126 because of grade 2 gastritis. One additional patient in the 150 mg after placebo group discontinued treatment in part 3 at week 60 because of a TEAE, but this TEAE (grade 2 mood swings) started in part 2 during week 26. All TEAEs leading to

TABLE II. Overall summary of TEAEs experienced by patients who entered part 3 of APeX-2

	TEAEs starting in part 1 or 2 (week 1 to week 48)				TEAEs starting in part 3 (week 48 up to week 240*)			
TEAE	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover
N	26	14	15	26	26	14	15	26
Any TEAE	26 (100)	14 (100)	14 (93.3)	24 (92.3)	20 (76.9)	11 (78.6)	13 (86.7)	23 (88.5)
Any drug-related TEAE	11 (42.3)	9 (64.3)	8 (53.3)	10 (38.5)	4 (15.4)	2 (14.3)	2 (13.3)	4 (15.4)
Any TESAE	1 (3.8)	4 (28.6)	2 (13.3)	0	1 (3.8)	2 (14.3)	2 (13.3)	2 (7.7)
Any drug-related TESAE	0	0	0	0	0	0	0	0
Any grade 3 or 4 TEAE	2 (7.7)	4 (28.6)	2 (13.3)	2 (7.7)	3 (11.5)	2 (14.3)	3 (20.0)	2 (7.7)
Any drug-related grade 3 or 4 TEAE	0	0	0	1 (3.8)	1 (3.8)	0	0	0
Any TEAE leading to interruption of study drug	1 (3.8)	1 (7.1)	3 (20.0)	0	2 (7.7)	0	2 (13.3)	1 (3.8)
Any TEAE leading to discontinuation of study drug	0	2 (14.3)†	0	0	1 (3.8)	1 (7.1)	0	1 (3.8)
Any drug-related investigator-identified rash‡	1 (3.8)	0	0	0	0	0	0	0
Any abdominal-related gastrointestinal TEAE§,‖	15 (57.7)	12 (85.7)	10 (66.7)	12 (46.2)	5 (19.2)	4 (28.6)	4 (26.7)	5 (19.2)
Any abdominal-related gastrointestinal TEAE leading to study drug discontinuation	0	1 (7.1)	0	0	1 (3.8)	1 (7.1)	0	0
Any abdominal-related gastrointestinal TEAE deemed to be drug related	10 (38.5)	8 (57.1)	7 (46.7)	8 (30.8)	1 (3.8)	0	0	3 (11.5)

Data are presented as n (%).
A drug-related TEAE was defined as any TEAE where the investigator defined the relationship as possibly related, probably related, or definitely related to study drug.
MedDRA, Medical Dictionary for Regulatory Activities; *TEAE*, treatment-emergent adverse event; *TESAE*, treatment-emergent serious adverse event.
*Although the protocol allowed treatment up to week 240, the longest a patient remained on study was up to week 188.
†One patient in the 150 mg after placebo group discontinued study drug in part 3 because of a TEAE that started in part 2.
‡Any drug-related investigator-identified rash was a TEAE of special interest.
§Abdominal-related gastrointestinal TEAEs were any TEAEs with a high-level group preferred term of *Gastrointestinal signs and symptoms* or *Gastrointestinal motility and defaecation conditions* (based on MedDRA v19.1).
‖Three patients who experienced abdominal-related gastrointestinal TEAE in part 3 had not experienced this type of TEAE in parts 1 and 2.

discontinuation in part 3 were deemed possibly or probably related to berotralstat treatment. The reasons behind the remaining discontinuations in part 3 are detailed in Figure 2.

Effectiveness

HAE attacks. In all treatment groups, adjusted subject-reported HAE attack rates decreased as early as the first 4 weeks of starting berotralstat treatment and thereafter were maintained or steadily decreased further with up to 96 weeks of continued treatment (Figure 3). For patients who completed 96 weeks of berotralstat treatment (n = 70), the mean (SEM) change in attack rate from baseline was −2.21 (0.20) attacks/mo at month 24. This value was −2.46 (0.35) attacks/mo for the 150 mg group (n = 21), −2.25 (0.37) attacks/mo for the 150 mg after placebo group (n=12), −1.94 (0.47) attacks/mo for the 110 to 150 mg crossover after placebo group (n = 13), and −2.12 (0.41) attacks/mo for the 110 to 150 mg crossover group (n = 24) (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). For patients who completed 96 weeks of berotralstat treatment in the 150 mg group, the

TABLE III. The most frequent TEAEs experienced by patients in part 3 of APeX-2

TEAE	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	All patients
N	26	14	15	26	81
Nasopharyngitis	7 (26.9)	3 (21.4)	3 (20.0)	3 (11.5)	16 (19.8)
Urinary tract infection	1 (3.8)	1 (7.1)	3 (20.0)	3 (11.5)	8 (9.9)
Abdominal pain	3 (11.5)	1 (7.1)	0	1 (3.8)	5 (6.2)
Arthralgia	3 (11.5)	1 (7.1)	1 (6.7)	0	5 (6.2)
Coronavirus infection	2 (7.7)	1 (7.1)	1 (6.7)	1 (3.8)	5 (6.2)
Diarrhea	2 (7.7)	1 (7.1)	1 (6.7)	1 (3.8)	5 (6.2)

Data are presented as n (%).
Frequent TEAEs are those that occurred in at least 5% of the total number of patients in the population.
TEAE, Treatment-emergent adverse event.

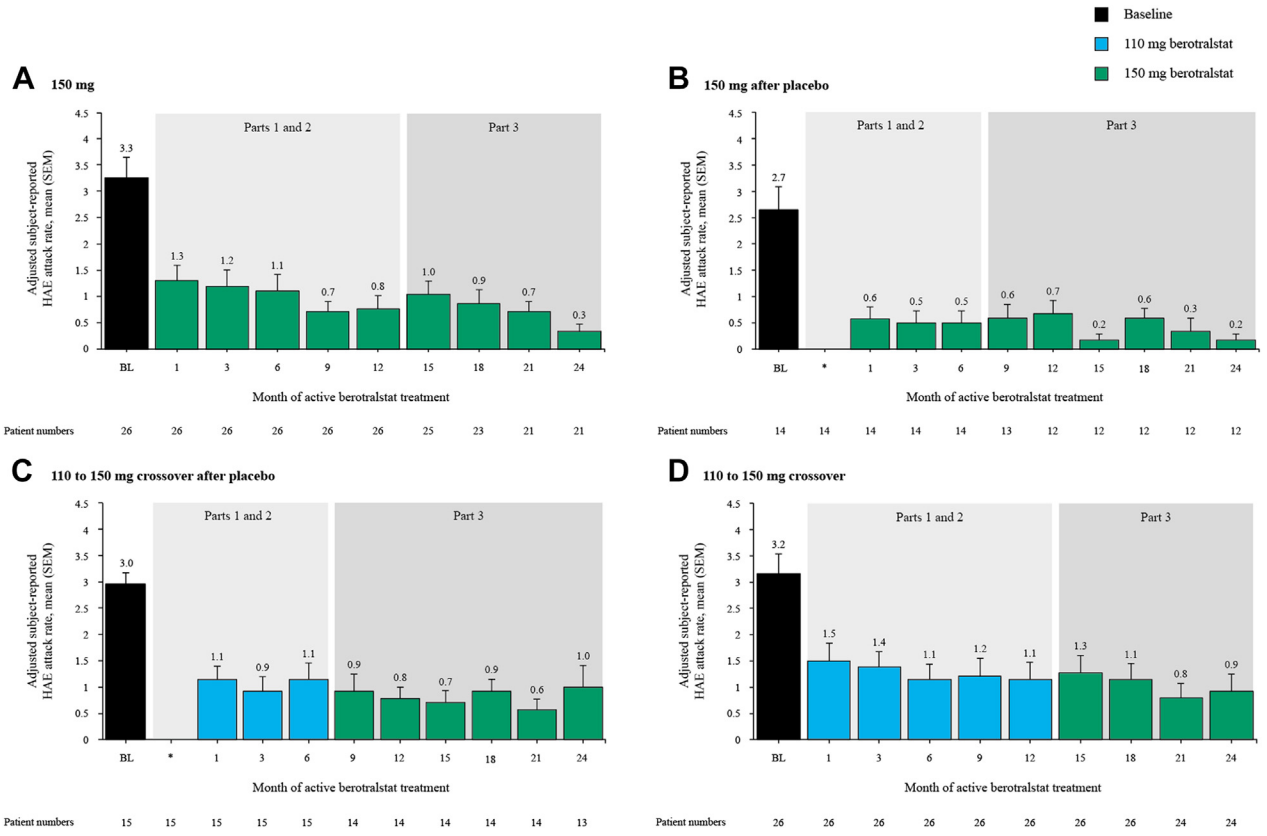

FIGURE 3. Mean adjusted subject-reported HAE attack rates over time for patients who entered part 3 of APeX-2 (n = 81). Mean adjusted subject-reported HAE attack rates from baseline to 96 weeks of berotralstat treatment for selected months for (**A**) the 150 mg group, (**B**) the 150 mg after placebo group, (**C**) the 110 to 150 mg crossover after placebo group, and (**D**) the 110 to 150 mg crossover group. Baseline adjusted subject-reported HAE attack rates are based on the number of HAE attacks experienced between screening and the start of part 1 (ie, the run-in period). *Patients in (**B**) and (**C**) received placebo for 6 months before starting berotralstat treatment; therefore, visits for these patients were adjusted according to the date of first dose of active treatment. Mean adjusted subject-reported attack rates after 6 months of placebo were 1.4 attacks/mo for the 150 mg after placebo group and 2.2 attacks/mo for the 110 to 150 mg crossover after placebo group. *BL*, baseline; *HAE*, hereditary angioedema; *SEM*, standard error of the mean.

average percentage reduction in attack rate from baseline was 90.8% at month 24.

During the 24th month of berotralstat treatment, all treatment groups had a median attack rate of zero (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). In the 150 mg group, the median attack rate was zero for 11 of the 12 months of part 3.

Individual patient attack rates for part 3 are shown in Figure E3 (available in this article's Online Repository at www.jaci-inpractice.org).

TABLE IV. HAE attack−free days during part 3 (week 48 to week 240*) of APeX-2

Variable	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	All patients
N	26	14	15	26	81
No. of attack-free days					
Mean	536.0	569.3	577.2	549.3	553.7
SEM	50.3	63.2	47.6	32.7	23.5
Median	583.5	650.0	623.0	582.5	587.0
Range	13-980	46-843	37-848	67-852	13-980
Percentage of attack-free days					
Mean	93.1	96.1	91.4	92.4	93.1
SEM	1.92	1.40	2.72	2.53	1.15
Median	97.5	98.3	96.5	96.5	97.2
Range	59-100	81-100	65-100	41-100	41-100
Total number of days on berotralstat in part 3					
Median	613.5	661.5	672	626	644
Range	22-981	50-856	49-868	162-890	22-981

Number of HAE attack−free days is based on adjusted subject-reported attacks.
HAE, Hereditary angioedema; *SEM*, standard error of the mean.
*Although the protocol allowed treatment up to week 240, the longest a patient remained on study was up to week 188.

HAE attack−free days and periods. In part 3, patients were attack free for 93.1% of the days (Table IV). The mean (SEM) number of attack-free days was similar across treatment groups and was 553.7 (23.5) days for all 81 patients.

Across the entire study, the mean (SEM) average number of days between attacks was 81.4 (14.0) days for all 81 patients. The maximum duration patients were attack free ranged from 15 to 1022 days. In the 150 mg group, the mean (SEM) average number of days between attacks was 80.9 (15.6) days, and the maximum duration patients were attack free ranged from 32 to 946 days.

On-demand medication use. Use of on-demand HAE medication declined rapidly, as early as the first 4 weeks of berotralstat treatment. Thereafter, prolonged treatment with berotralstat led to further reductions, with the mean adjusted number of doses per month being less than 1.25 in all treatment groups at the 24th month of treatment.

In the 150 mg group, the mean (SEM) adjusted number of doses per month decreased from 3.8 (0.76) at baseline (n = 26) to 0.4 (0.18) at the 24th month (n = 21). For patients in this group who completed 96 weeks of berotralstat treatment (n = 21), the mean (SEM) change from baseline was −2.4 (0.51) doses/mo at month 24 (average percentage reduction: 88.5%; n = 19 because 2 patients did not receive any on-demand dose at baseline).

Patient-reported outcomes

Quality of life. Overall, patients reported an improvement in their QoL throughout 96 weeks of treatment with berotralstat, with improvements being observed early after treatment initiation (Figure 4). At 96 weeks of berotralstat treatment, improvements from baseline (or placebo) were observed across all treatment groups and domains of the AE-QoL except for the *fatigue/mood* domain in the 110 to 150 mg crossover after placebo group.

At 96 weeks of berotralstat treatment, all treatment groups showed clinically meaningful improvements (reductions exceeding the MCID) from baseline (or placebo) in the mean AE-QoL total score, and at this time point, 70.6% of patients (n = 48/68) had a clinically meaningful improvement.

The 150 mg group showed the largest improvements across all domains. Among patients in this group who completed 96 weeks of berotralstat treatment, the mean (SEM) change from baseline (n = 19) was −22.97 (3.57) points in the AE-QoL total score ($P < .0001$), −18.68 (4.98) points in the *fatigue/mood* domain ($P = .0019$), −21.05 (4.37) points in the *fear/shame* domain ($P = .0005$), −33.44 (6.08) points in the *functioning* domain ($P = .0001$), and −19.08 (4.62) points in the *nutrition* domain ($P = .0010$) (Figure E4, available in this article's Online Repository at www.jaci-inpractice.org). In the other treatment groups, the largest improvement was also observed in the *functioning* domain.

Treatment satisfaction. Throughout 96 weeks of treatment with berotralstat, treatment satisfaction generally improved in all treatment groups over all domains of the TSQM (Figure E5, available in this article's Online Repository at www.jaci-inpractice.org). The largest improvement in both the 150 mg group and the 110 to 150 mg crossover group was observed in the *convenience* domain. For patients in these groups who completed 96 weeks of berotralstat treatment, the mean (SEM) change from baseline in this domain was +34.6 (5.98) points ($P < .0001$; n = 18) and +22.9 (5.58) points ($P = .0007$; n = 24), respectively. In the 2 groups that received placebo for 6 months on entry into part 1, the largest improvement was observed in the *global satisfaction* score. The 150 mg after placebo group and the 110 to 150 mg crossover after placebo group showed mean (SEM) changes from placebo to 96 weeks of berotralstat treatment of +17.3 (8.18) points ($P = .0518$; n = 12) and +23.1 (8.49) points ($P = .0195$; n = 13), respectively. Despite differences in the level of improvement from baseline (or placebo), the *global satisfaction* scores after 96 weeks of berotralstat treatment were similar across all treatment groups. Across all treatment groups, large improvements were also seen in the *effectiveness* domain.

DISCUSSION

The results from this open-label extension of APeX-2 are consistent with the safety and efficacy results observed in parts 1

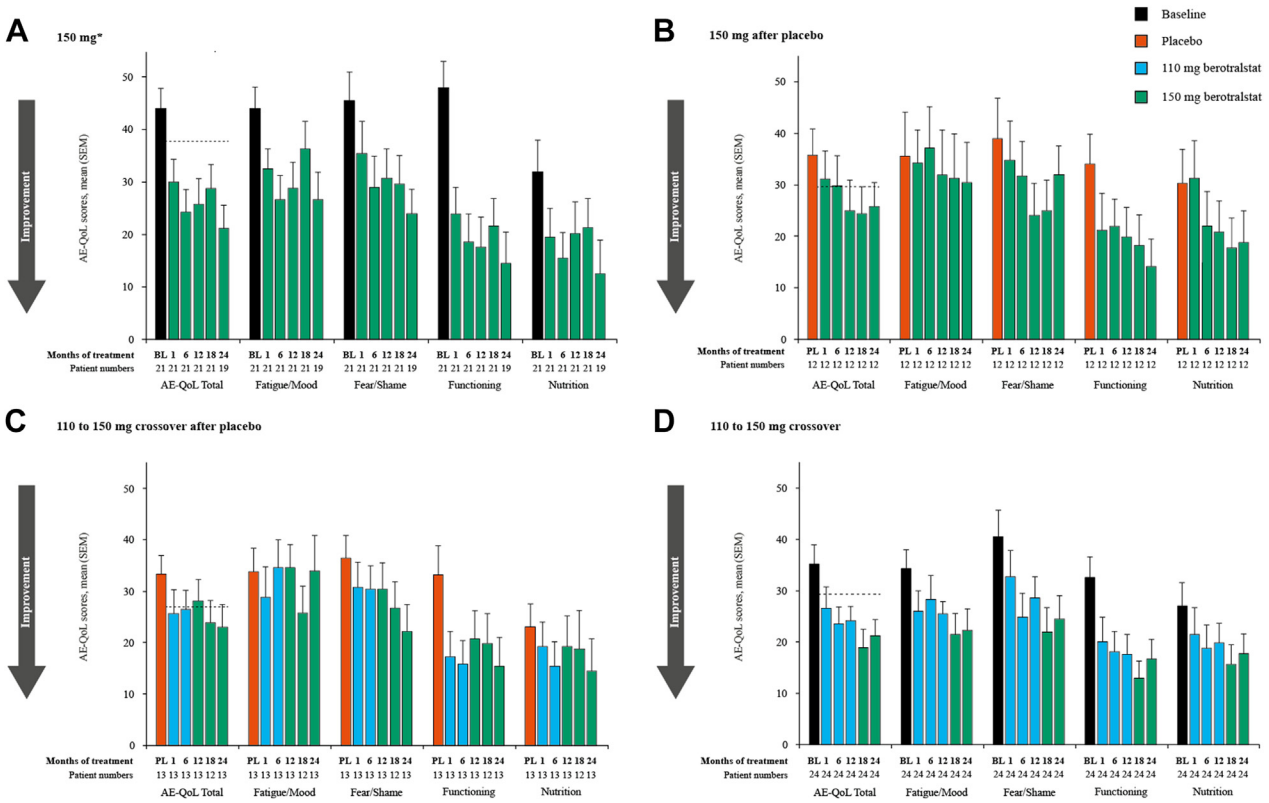

FIGURE 4. Mean AE-QoL scores over time for patients who entered part 3 of APeX-2 (n = 81). Mean AE-QoL scores by domain over time for (**A**) the 150 mg group, (**B**) the 150 mg after placebo group, (**C**) the 110 to 150 mg crossover after placebo group, and (**D**) the 110 to 150 mg crossover group. BL values represent values on day 1. PL values are after 6 months on placebo. "Months of treatment" represents months on active berotralstat treatment. For patients who received placebo for 6 months before starting berotralstat treatment (ie, **B** and **C**), visits were adjusted according to the date of first dose of active treatment. As per the protocol, the AE-QoL was not administered at all visits. The black dotted line represents the MCID. *AE-QoL*, Angioedema Quality of Life questionnaire; *BL*, baseline; *MCID*, minimal clinically important difference; *PL*, placebo; *SEM*, standard error of the mean.

and 2 and support the long-term benefits of prophylactic treatment with oral berotralstat, including improvements in QoL. Apart from underrepresentation of non-White races, participants in APeX-2 were broadly representative of patients living with HAE.

No new safety signals appeared in part 3 of APeX-2, with most TEAEs being mild or moderate. In part 3, no drug-related TESAEs were reported, and less than 5% of patients discontinued treatment because of TEAEs. Drug-related abdominal-related gastrointestinal TEAEs occurred in a considerably lower percentage of the patients in part 3 (4.9%) than in the same patients in parts 1 and 2 (40.7%). This is in line with previous reports stating that abdominal-related gastrointestinal TEAEs typically occur early during the treatment course.[25] Furthermore, abdominal-related gastrointestinal TEAEs have been reported to be generally mild and self-limiting in nature.[25,26] Importantly, the patient-reported TSQM scores for the *side effects* domain remained consistently high with continued berotralstat treatment, suggesting long-term tolerability.

Patients who remained on study in part 3 experienced further reductions in monthly HAE attack rates beyond what occurred in parts 1 and 2, suggesting that response to berotralstat prophylaxis is durable. Specifically, the 67% and 52% reduction from baseline observed in part 2 for the 150 mg (n = 31) and 110 mg groups (n = 28),[18] respectively, increased to 90.8% (n = 21) and 74.9% (n = 24) in part 3 after 96 weeks of continued berotralstat treatment. Accordingly, patients across all treatment groups were attack-free for 93.1% of the days in part 3. Reductions in HAE attack rates were also accompanied by reductions in on-demand medication use across all treatment groups (88.5% reduction in the 150 mg group after 96 weeks), further adding to the benefit of berotralstat prophylaxis. Reducing the rate of HAE attacks and achieving disease control are the goals of long-term prophylaxis in patients with HAE.[12,27] This is paramount because it lessens disease burden, reduces QoL impairment, and helps normalize patients' lives.[12,28]

HAE attacks can interfere with patients' work, school, family, and social and physical activities, thereby greatly affecting their QoL.[28] In this study, the largest improvements in QoL were observed in the *functioning* domain, suggesting that treatment with berotralstat may have a positive impact on patients' ability to perform day-to-day activities. Generally, smaller improvements in AE-QoL scores were observed in the groups that had been treated with placebo for 6 months, likely because of a placebo effect on QoL. Indeed, these groups generally had lower values after placebo treatment than the non-placebo groups had

at baseline, suggesting that 6 months of daily treatment with oral placebo before starting berotralstat prophylaxis may have already led to improvements in QoL.

Although various prophylactic treatments are available for HAE, all recommended first-line options except berotralstat are parenteral therapies.[12] Parenteral therapies can place a treatment burden on patients[29,30] and can be associated with clinical challenges such as venous access, injection-site pain, and infection.[16,31] In fact, one study found that 68% of patients with HAE felt that injections or infusions were unpleasant, and that most patients desired novel therapies with simpler administration routes.[32] Oral therapies have the potential to reduce this treatment burden,[28] and the data presented here show that long-term prophylaxis with oral berotralstat QD leads to improvements across all patient satisfaction domains, including *convenience*. Importantly, smaller improvements in the *convenience* domain were seen for the placebo groups because baseline values for these groups represent patient reflections after already having received daily oral medication (ie, placebo). Similar improvements in TSQM scores were also reported in the long-term, open-label APeX-S study.[33] Thus, treatment with berotralstat has the potential to minimize the treatment burden versus that typically associated with injectable prophylactic and on-demand medicines while simultaneously reducing HAE attack frequency.

The small number of patients in each treatment group was a limitation of APeX-2 part 3 and resulted in variability. Furthermore, analyses beyond 96 weeks of treatment were limited by the fact that 40 patients discontinued the study once berotralstat became commercially available. Hypothesis testing and statistical analyses were not prespecified in the protocol for part 3, and as such conclusions around the significance of changes from baseline cannot be made. Selection bias for less severe patients and patients who respond well to study drug is a limitation of long-term open-label studies and may have occurred over the course of this study as patients who experienced tolerability issues or limited efficacy with berotralstat dropped out. Nonetheless, in part 3, most patients discontinued to receive commercial berotralstat. These factors, combined with the observed placebo effect on QoL measures, should be considered when drawing conclusions about the data presented here.

In this long-term extension of APeX-2, oral administration of berotralstat QD was generally well tolerated and showed no new safety signals in patients with type 1 or type 2 HAE. Patients who were treated with berotralstat for 96 weeks experienced a durable response that increased over time, with both considerable reductions in the number of monthly HAE attacks and clinically relevant improvements in QoL occurring across all treatment groups. The long-term data presented here reinforce findings from other berotralstat studies and support the use of oral berotralstat as an effective, convenient treatment option for patients living with HAE.

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ONLINE REPOSITORY

METHODS

Full list of inclusion criteria for APeX-2

Main criteria for inclusion:

- Males and non-pregnant, non-lactating females ≥18 years of age (main study) or ≥12 to 17 years of age (substudy).
- Able to provide written, informed consent. Patients aged 12 to 17 years who are screening for the substudy must be able to read, understand, and be willing to sign an assent form in addition to a caregiver providing informed consent.
- Patient weight of ≥40 kg.
- A clinical diagnosis of hereditary angioedema 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, patient is not having an hereditary angioedema [HAE] attack), one of the following is acceptable to confirm the diagnosis of HAE: (1) a *SERPING1* gene mutation known or likely to be associated with type 1 or 2 HAE assessed during the screening period, (2) a confirmed family history of C1-INH deficiency, and (3) a C4 redrawn and retested during an attack in the screening period with the results below the LLN reference range.
  - For patients with C1-INH function ≥50% but less than the assay LLN, a *SERPING1* gene mutation known or likely to be associated with type 1 or 2 HAE, as assessed during the screening period, or a repeat C1-INH functional level <50% will be considered acceptable for enrollment.
- 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 the acute treatment of HAE attacks is an acceptable medication for this purpose.
- Patients must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study.
- The patient must have at least 2 HAE attacks that meet all the requirements below 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 have either been treated, required medical attention, or be documented to cause functional impairment based on patient entry in the diary. Functional impairment is defined as the patient not being able to perform their daily activities without restriction (ie, patient 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, which are indicative of internal swelling.
  - The attacks are otherwise confirmed by the investigator to be HAE attacks.
  - Patients who have recorded 2 such attacks may be randomized to receive study drug beginning on or after day 28 of the run-in period; patients who have recorded at least 3 such attacks may be randomized 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 study patients.
- Female and male patients must agree to the contraception requirements and must meet the inclusion criteria regarding contraception, and contraception of female partners (as applicable). Note: contraception is no longer required for male patients and their female partners under Protocol Version 3.0.
- In the opinion of the investigator, the patient is expected to adequately comply with all required study procedures for the duration of the study. The patient 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.

Full list of exclusion criteria for APeX-2

- Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the investigator or sponsor, would interfere with the patient's ability to participate in the study or increases the risk to the patient by participating in the study.
- 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.
- Anticipated use of short-term prophylaxis of angioedema attacks for a preplanned procedure during the screening or study periods (parts 1 and 2 only).
- Concurrent diagnosis of any other type of recurrent angioedema.
- Clinically significant abnormal electrocardiogram at the screening visit. This includes, but is not limited to, a corrected QT interval using Fridericia's method (QTcF) >470 ms for women, a QTcF >450 ms for men, PR interval >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.
- 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.
- Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
- History of or current implanted defibrillator or pacemaker.
- 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 aspartate aminotransferase or alanine aminotransferase value ≥3 times the upper limit of the normal reference range value obtained during screening is exclusionary.
- Prior enrollment in a BCX7353 study.
- Suspected C1-INH resistance in the opinion of the investigator or sponsor.

- History of alcohol or drug abuse within the previous year before the screening visit or current evidence of substance dependence or abuse (self-reported alcohol intake >3 drinks/d).
- Positive serology for human immunodeficiency virus or current infection with hepatitis B virus or hepatitis C virus.
- Pregnant, planning to become pregnant during the study, or nursing.
- Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).
- History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.
- Use of androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days before the screening visit or initiation during the study.
- Use of C1-INH for prophylaxis of HAE attacks within the 14 days before 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.
- Use of concomitant medications that are metabolized by cytochrome (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.
- 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 before the baseline visit or planned initiation during the study.
- Use of a medication that is transported by P glycoprotein and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.
- Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
- 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).
- Current participation in any other investigational drug study or received another investigational drug within 30 days of the screening visit.
- An immediate family relationship to either sponsor employees, the investigator, or employees of the study site named on the delegation log.
- Held in an institution by a government or judicial order.

Assessments and reporting of attacks

Treatment-emergent adverse events (TEAEs) were assessed and recorded from the time of informed consent through to the last follow-up visit or until the TEAE resolved.

In part 3, patient-reported outcome assessments were conducted every 12 weeks from week 60 to week 240. The Treatment Satisfaction Questionnaire for Medication was only administered every 24 weeks starting from week 96.

All patients recorded (on a daily basis) the frequency, duration, location, functional impact or severity, and any treatment of HAE attacks. Unlike in parts 1 and 2, during which attack data were collected in an e-diary, patients in part 3 collected data in a paper diary. Although investigators did not confirm attacks in part 3, all recorded attacks were reviewed and accepted or rejected according to a set of predefined rules constructed in concert with HAE-treating physicians. Accordingly, adjusted subject-reported attacks included those subject-reported attacks that met the following criteria:

- The attack had at least 1 symptom of swelling
- The attack had a response of "no" to the diary question "In retrospect, could there be an alternative explanation for your symptoms other than an HAE attack (ie, allergic reaction, viral cold, etc)?"
- The attack was unique (ie, it began >24 hours from the end of the prior attack), and
- The attack had a duration of >24 hours if untreated.

Adjusted subject-reported attacks occurring in parts 1 and 2 of the study were also determined using the same criteria to enable comparison of the same outcome measure over time. As such, all HAE attacks reported in this paper are adjusted subject-reported attacks. In contrast, HAE attack data published separately in the part 1 and 2 papers are investigator-confirmed attacks.[E1,E2]

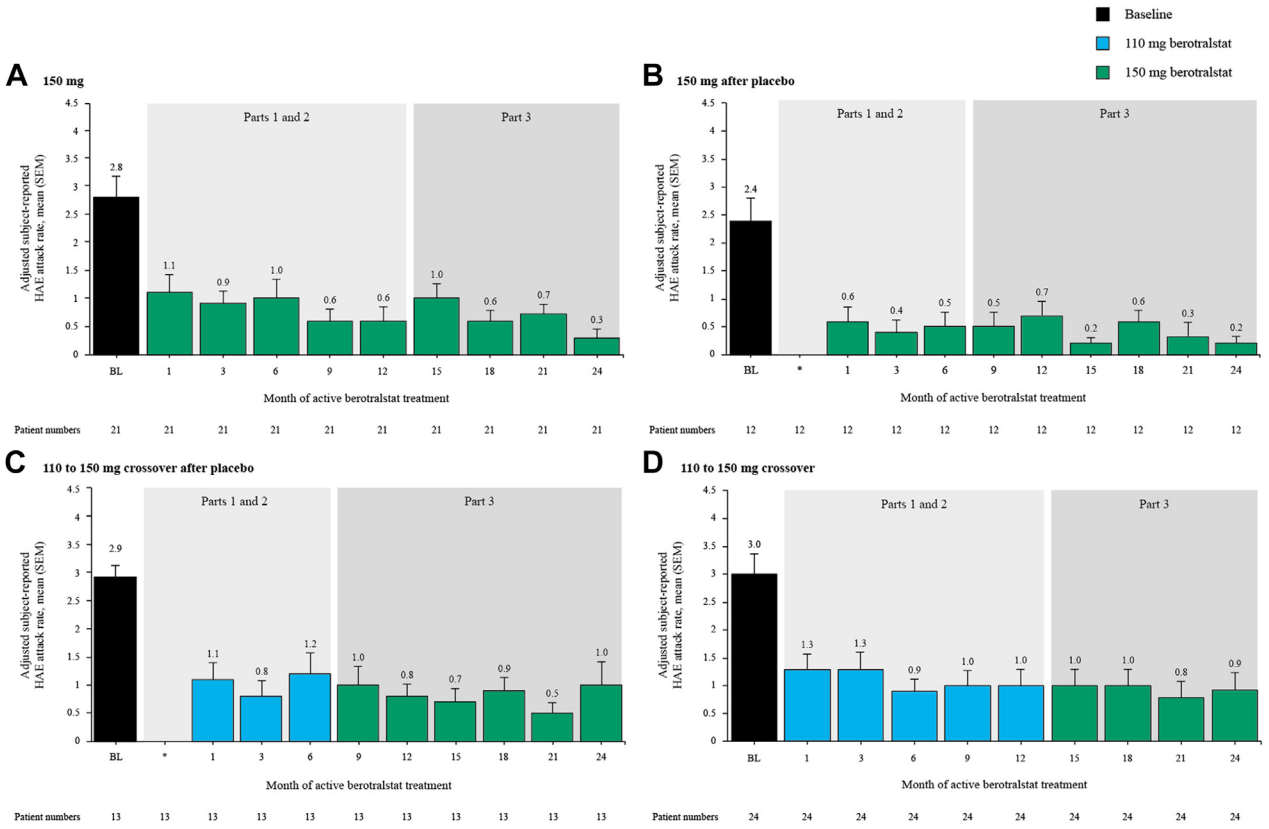

FIGURE E1. Mean adjusted subject-reported HAE attack rates over time for patients who entered part 3 of APeX-2 and completed 96 weeks of berotralstat treatment (n = 70). Mean adjusted subject-reported HAE attack rates from baseline to 96 weeks of berotralstat treatment for the 96-week completers from (**A**) the 150 mg group, (**B**) the 150 mg after placebo group, (**C**) the 110 to 150 mg crossover after placebo group, and (**D**) the 110 to 150 mg crossover group. Baseline adjusted subject-reported HAE attack rates are based on the number of HAE attacks experienced between screening and the start of part 1 (ie, the run-in period). *Patients in (**B**) and (**C**) received placebo for 6 months before starting berotralstat treatment; therefore, visits for these patients were adjusted according to the date of first dose of active treatment. Mean adjusted subject-reported attack rates after 6 months of placebo were 1.2 attacks/mo for the 150 mg after placebo completers group and 2.3 attacks/mo for the 110 to 150 mg crossover after placebo completers group. *BL*, baseline; *HAE*, hereditary angioedema; *SEM*, standard error of the mean.

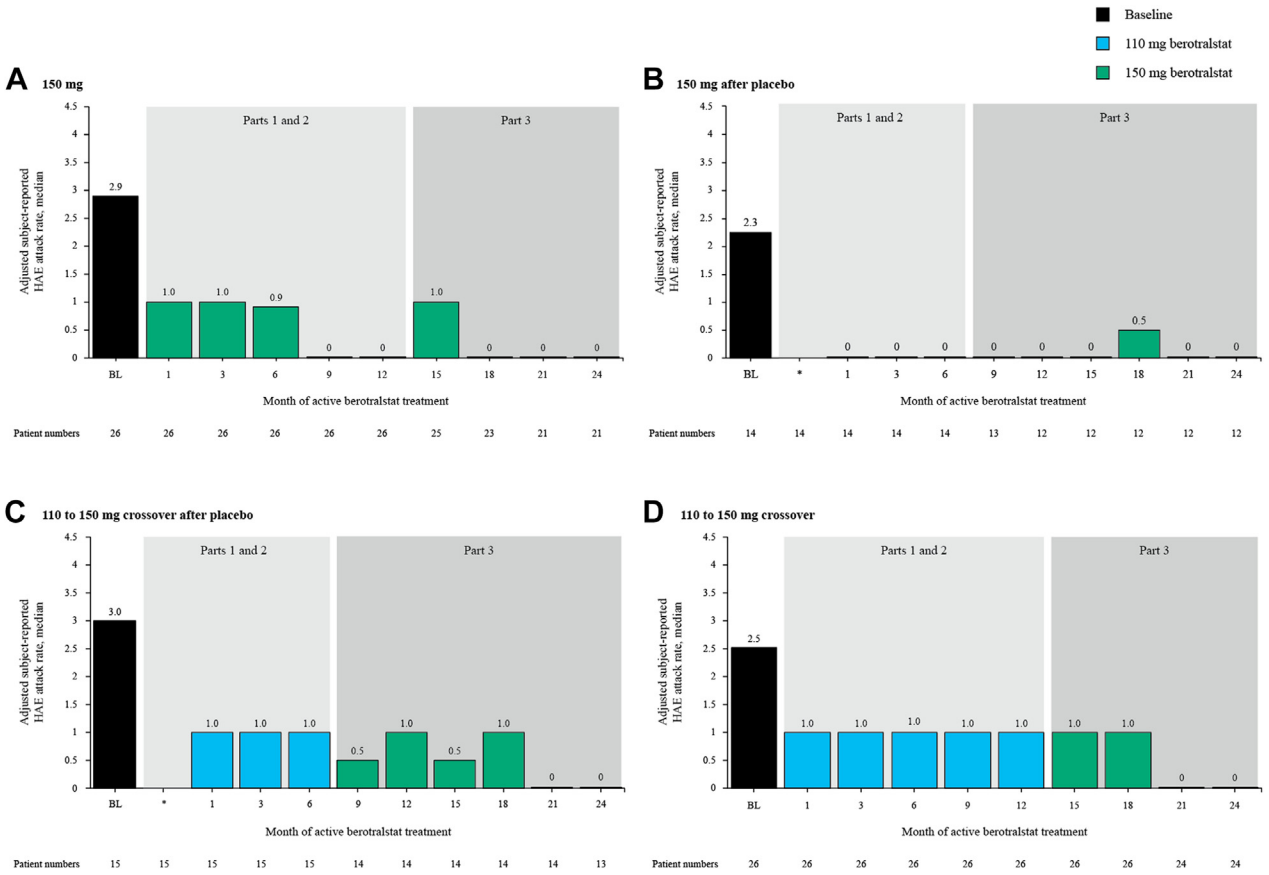

FIGURE E2. Median adjusted subject-reported HAE attack rates over time for patients who entered part 3 of APeX-2 (n = 81). Median adjusted subject-reported HAE attack rates over time for (**A**) the 150 mg group, (**B**) the 150 mg after placebo group, (**C**) the 110 to 150 mg crossover after placebo group, and (**D**) the 110 to 150 mg crossover group. Baseline adjusted subject-reported HAE attack rates are based on the number of HAE attacks experienced between screening and the start of part 1 (ie, the run-in period). *Patients in (**B**) and (**C**) received placebo for 6 months before starting berotralstat treatment; therefore, visits for these patients were adjusted according to the date of first dose of active treatment. Median adjusted subject-reported attack rates after 6 months of placebo were 1.0 attacks/mo for the 150 mg after placebo group and 2.0 attacks/mo for the 110 to 150 mg crossover after placebo group. *BL*, baseline; *HAE*, hereditary angioedema.

	Study Month									Completed study*
	13	16	19	22	25	28	31	34	36	
150 mg										
Patient 1†	0	1	4	1	0	0	3	0	1.93	**No***
Patient 2†	1	0	0	2	1	2	1	4	2.43	**No***
Patient 3‡	0	0	0	0	0	0	0			No
Patient 4§	3	1	0							No
Patient 5†	1	0	0	0	1	0	0	0		No
Patient 6†	0	0	1	0	0	0	0			No
Patient 7‡	0	0								No
Patient 8‡	0	0	3	1	5	3	4	3	4	No
Patient 9‖	1	2								No
Patient 10	0	1	0	0	0	0	0	1		Yes^x
Patient 11#	1	0								No
Patient 12‡	4.15									No
Patient 13	1	0	0	0	0	0	0	0	0	Yes
Patient 14†	2	1	1	1	1	1	0	0		No
Patient 15†	0	0	0	0	0	1	0	0		No
Patient 16†	0	0	0	0	0	0	0			No
Patient 17	0	0	0	0	0	0	0	0	0	Yes
Patient 18	3	0	0	1	1	4	4	4	2	Yes
Patient 19†	0	0	0	0	0	0	1	0	0	**No***
Patient 20†	1	0	1	1	1	0	0	0	0	**No***
Patient 21§	0	2	1	2	0	2				No
Patient 22†	1	0	0	1	0	0	0	0	0	**No***
Patient 23†	0	0	0	0	0	0	0	0	0	**No***
Patient 24**	0	0	0	0	0	0				No
Patient 25†	2	3	2	1	1	2	2	3	5	**No***
Patient 26†	0	1	0	0	1	0	0	0	0	**No***
150 mg after placebo										
Patient 1†	2	0	0	0	0	1	1	0	0	**No***
Patient 2†	2	2	1	1	0	0	0	0	0	**No***
Patient 3†	0	1	2	0	0	0	0	0		No
Patient 4	0	0	0	0	0	0	0	0	0	Yes
Patient 5†	2	0	2	2	0	0	1			No
Patient 6	0	0	0	0	0	0	0	0	0	Yes
Patient 7†	3	1	2	2	2	3	4			No
Patient 8‖	2									No
Patient 9	0	0	0	1	0	0	0	0	1.47	Yes
Patient 10	0	0	0	0	0	0	0	0	0	Yes
Patient 11‡	0	0	0	0	0	0	1	0		No
Patient 12†	0	1	0	0	1	1	0	0	0	**No***
Patient 13‖	0									No
Patient 14†	0	0	0	0	0	0	0	0	0	**No***
110 to 150 mg crossover after placebo										
Patient 1†	1	1	0	0	1	0	0			No
Patient 2	1	0	1	0	0	0	0	0	0	Yes
Patient 3†	4	3	2	3	1	0	3			No
Patient 4	0	0	1	1	1	2	0	1	1	Yes
Patient 5†	0	0	0	0	0	0	0	0		No
Patient 6§	4									No
Patient 7#	0	0	0	0	1	1				No
Patient 8	0	2	0	0	0	0	2	3	1.12	Yes
Patient 9	0	0	0	2	0	0	0	0	1	Yes
Patient 10	0	0	0	0	0	0	0	0	0	Yes
Patient 11†	1	0	2	0	0	0	0	0	0	**No***
Patient 12†	2	0	1	0	1	0	1	0	0	**No***
Patient 13§	2	4	1	3	4	3	3	3		No
Patient 14†	1	2	0	1	1	1	1	1	1	**No***
Patient 15†	0	0	0	0	0	1	0	0	0	**No***
110 to 150 mg crossover										
Patient 1†	1	1	0	0	0	1	0	1	0	**No***
Patient 2§	7	6								No
Patient 3†	2	2	1	2	0	0	1	0	0	**No***
Patient 4	0	0	2	1	1	0	2	2	0	Yes
Patient 5§	0	1	0							No
Patient 6	0	0	1	0	0	0	0	0	0	Yes
Patient 7†	2	2	2	2	1	2	0			No
Patient 8†	1	0	0	1	0	2	0			No
Patient 9†	3	0	1	1	0	0	0			No
Patient 10†	0	0	0	0	1	0	0			No
Patient 11†	0	0	0	0	0	0	0			No
Patient 12	0	1	0	0	0	2	0	0	0	Yes
Patient 13†	0	1	0	0	0	0	0	0		No
Patient 14‖	0	0	0	0	1	0	0			No
Patient 15	3	2	0	3	1	1	1	0	1	Yes
Patient 16	0	0	0	0	0	0	0	0	0	Yes
Patient 17†	1	1	0	0	0	0	0	0		No
Patient 18	0	0	1	0	0	0	1	0	0	Yes
Patient 19	1	0	0	0	0	0	0	0	1	Yes
Patient 20†	0	0	0	0	0	0	0			No
Patient 21‡	3	2	2	2						No
Patient 22†	3	0	0	0	0	0	0			No
Patient 23††	6	5	6	5	4	6	5	5	6	**No***
Patient 24†	3	4	4	3	3	5	6	5		No
Patient 25**	0	1	0	2	0					No
Patient 26†	1	1	0	0	1	2	0	0	0	**No***

Adjusted subject-reported HAE attack rate

Key

0 1 2 3 4 5 6 7

FIGURE E3. Individual adjusted subject-reported HAE attack rates during part 3 (n = 81). The heat map shows adjusted subject-reported HAE attack rates during part 3 for each of the 81 patients. Study month corresponds to the actual study month and is not adjusted to the month of active berotralstat treatment. *Patients who enrolled under the original protocol were considered to have completed the study upon reaching month 36 (week 144). However, some patients (n = 20) reached or continued past month 36 (week 144) but were not considered to have completed the study because they enrolled after a protocol amendment extended the study to up to 60 months (240 weeks). †Discontinued study treatment to receive berotralstat via another mechanism. ‡Discontinued study treatment due to withdrawal of consent. §Discontinued study treatment due to perceived lack of efficacy. ‖Discontinued study treatment because of a laboratory abnormality or TEAE. #Discontinued study treatment due to recurrent illness, emergence of new illness, or a medical condition or pregnancy. **Discontinued study treatment due to some "other" reason. ††Discontinued study treatment due to sponsor decision. ^xThis patient was considered to have completed the study because their final visit was within the allowed window of month 36. *HAE*, hereditary angioedema; *TEAE*, treatment-emergent adverse event.

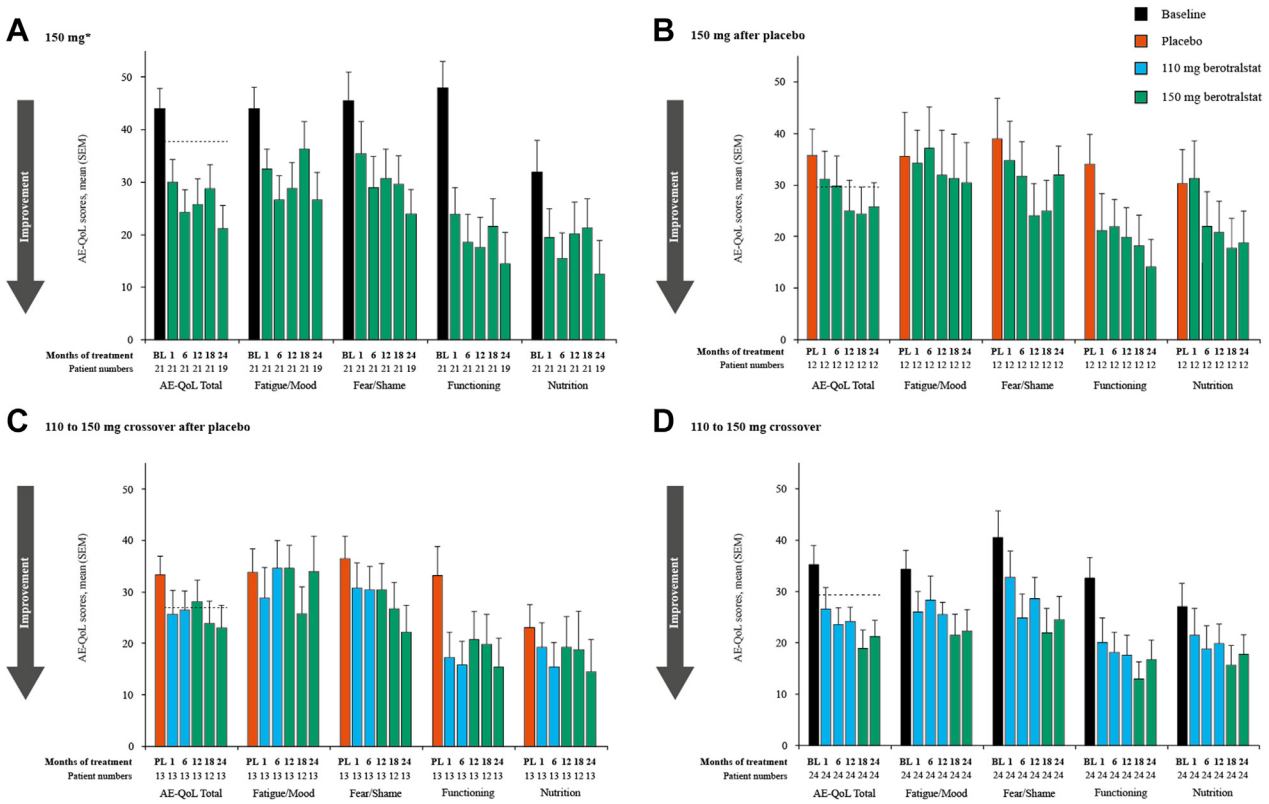

FIGURE E4. Mean AE-QoL scores over time for patients who entered part 3 of APeX-2 and completed 96 weeks of berotralstat treatment (n = 70). Mean AE-QoL scores by domain over time for the 96-week completers from (**A**) the 150 mg group, (**B**) the 150 mg after placebo group, (**C**) the 110 to 150 mg crossover after placebo group, and (**D**) the 110 to 150 mg crossover group. BL values represent values on day 1. PL values are after 6 months on placebo. "Months of treatment" represents months on active berotralstat treatment. For patients who received placebo for 6 months before starting berotralstat treatment (ie, **B** and **C**), visits were adjusted according to the date of first dose of active treatment. As per the protocol, the AE-QoL was not administered at all visits. The black dotted line represents the MCID. *Two patients in the 150 mg group did not complete the questionnaire at 96 weeks of treatment. *AE-QoL*, Angioedema Quality of Life questionnaire; *BL*, baseline; *MCID*, minimal clinically important difference; *PL*, placebo; *SEM*, standard error of the mean.

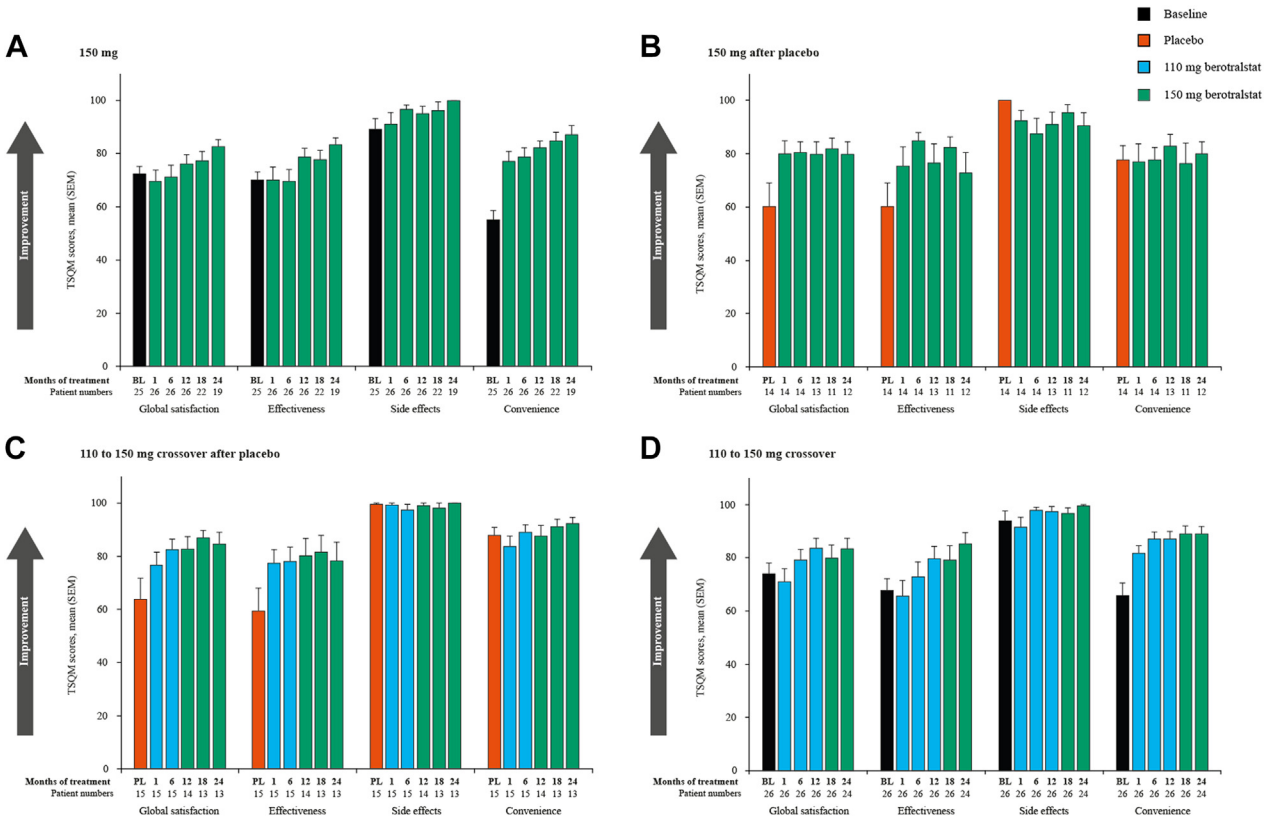

FIGURE E5. Mean TSQM scores over time for patients who entered part 3 of APeX-2 (n = 81). Mean TSQM scores by domain over time for (**A**) the 150 mg group, (**B**) the 150 mg after placebo group, (**C**) the 110 to 150 mg crossover after placebo group, and (**D**) the 110 to 150 mg crossover group. BL values represent values on day 1. PL values are after 6 months on placebo. "Months of treatment" represents months on active berotralstat treatment. For patients who received placebo for 6 months before starting berotralstat treatment (ie, **B** and **C**), visits were adjusted according to the date of first dose of active treatment. As per the protocol, the TSQM was not administered at all visits. *BL*, baseline; *PL*, placebo; *SEM*, standard error of the mean; *TSQM*, Treatment Satisfaction Questionnaire for Medication.

TABLE E1. List of study site locations and principal investigators

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

TABLE E2. Discontinuations in parts 1 and 2 of APeX-2

	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	Placebo
Part 1 (weeks 1-24)					
Illness/condition	0	N/A	N/A	0	0
Perceived lack of efficacy	1	N/A	N/A	1	2
Lab abnormality or TEAE	1	N/A	N/A	3	1
Withdrew consent	1	N/A	N/A	0	1
Investigator judgment	0	N/A	N/A	0	0
Noncompliance	0	N/A	N/A	0	0
Other	0	N/A	N/A	0	1
Part 2 (weeks 24-48)					
Illness/condition	0	0	0	1	N/A
Perceived lack of efficacy	3 + 2*	2	0	5	N/A
Lab abnormality or TEAE	2	0	0	1	N/A
Withdrew consent	1*	1	2	1	N/A
Investigator judgment	0	0	0	1	N/A
Noncompliance	0	0	0	1*	N/A
Other	1 + 2*	0	0	1*	N/A

Data are presented as number of discontinuations (n).
N/A, Not applicable; *TEAE*, treatment-emergent adverse event.
*Denotes 7 patients who completed dosing to week 48 but discontinued at the week 48 visit and therefore did not continue into part 3.

TABLE E3. Drug-related TEAEs experienced by patients in part 3 of APeX-2

	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	All patients
N	26	14	15	26	81
Gastrointestinal disorders	2 (7.7)	2 (14.3)	2 (13.3)	4 (15.4)	10 (12.3)
Abdominal pain	2 (7.7)	1 (7.1)	0	1 (3.8)	4 (4.9)
Abdominal discomfort	0	1 (7.1)	1 (6.7)	0	2 (2.5)
Diarrhea	1 (3.8)	1 (7.1)	0	0	2 (2.5)
Abdominal distension	0	0	0	1 (3.8)	1 (1.2)
Abdominal pain upper	1 (3.8)	0	0	0	1 (1.2)
Constipation	1 (3.8)	0	0	0	1 (1.2)
Dyspepsia	0	0	1 (6.7)	0	1 (1.2)
Gastritis	0	0	0	1 (3.8)	1 (1.2)
Gastroesophageal reflux disease	0	0	0	1 (3.8)	1 (1.2)
Nausea	0	0	0	1 (3.8)	1 (1.2)
Musculoskeletal and connective tissue disorders	1 (3.8)	0	1 (6.7)	0	2 (2.5)
Arthralgia	1 (3.8)	0	0	0	1 (1.2)
Muscle spasms	0	0	1 (6.7)	0	1 (1.2)
Ear and labyrinth disorders	1 (3.8)	0	0	0	1 (1.2)
Ear pain	1 (3.8)	0	0	0	1 (1.2)
Infections and infestations	1 (3.8)	0	0	0	1 (1.2)
Sinusitis	1 (3.8)	0	0	0	1 (1.2)
Psychiatric disorders	1 (3.8)	0	0	0	1 (1.2)
Libido decreased	1 (3.8)	0	0	0	1 (1.2)

Data are presented as n (%).
TEAEs recorded by the investigator as possibly related, probably related, or definitely related to study drug. TEAEs were coded using MedDRA v19.1 System Organ Class and Preferred Term.
MedDRA, Medical Dictionary for Regulatory Activities; *TEAE*, treatment-emergent adverse event.

TABLE E4. Grade 3 or 4 TEAEs experienced by patients in part 3 of APeX-2

	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	All patients
N	26	14	15	26	81
Infections and infestations	0	2 (14.3)	1 (6.7)	0	3 (3.7)
Gastroenteritis	0	1 (7.1)	0	0	1 (1.2)
Pneumonia	0	0	1 (6.7)	0	1 (1.2)
Pyelonephritis	0	1 (7.1)	0	0	1 (1.2)
Cardiac disorders	1 (3.8)	0	1 (6.7)	0	2 (2.5)
Acute myocardial infarction	1 (3.8)	0	0	0	1 (1.2)
Atrial fibrillation	0	0	1 (6.7)	0	1 (1.2)
Gastrointestinal disorders	1 (3.8)	0	0	1 (3.8)	2 (2.5)
Abdominal pain	1 (3.8)	0	0	0	1 (1.2)
Alcoholic gastritis	0	0	0	1 (3.8)	1 (1.2)
General disorders/administration site conditions	1 (3.8)	0	0	0	1 (1.2)
Vascular stent occlusion	1 (3.8)	0	0	0	1 (1.2)
Musculoskeletal and connective tissue disorders	1 (3.8)	0	0	0	1 (1.2)
Musculoskeletal chest pain	1 (3.8)	0	0	0	1 (1.2)
Nervous system disorders	0	0	0	1 (3.8)	1 (1.2)
Sinus headache	0	0	0	1 (3.8)	1 (1.2)
Psychiatric disorders	0	0	1 (6.7)	0	1 (1.2)
Bipolar disorder	0	0	1 (6.7)	0	1 (1.2)

Data are presented as n (%).
TEAEs were coded using MedDRA v19.1 System Organ Class and Preferred Term.
MedDRA, Medical Dictionary for Regulatory Activities; *TEAE*, treatment-emergent adverse event.

TABLE E5. Grade 3 or 4 laboratory abnormalities experienced by patients in part 3 of APeX-2

	150 mg	150 mg after placebo	110 to 150 mg crossover after placebo	110 to 150 mg crossover	All patients
N	26	14	15	26	81
Any grade 3 or 4 laboratory abnormality	3 (11.5)	1 (7.1)	1 (6.7)	3 (11.5)	8 (9.9)
Grade 3	3 (11.5)	0	1 (6.7)	3 (11.5)	7 (8.6)
Grade 4	0	1 (7.1)	0	0	1 (1.2)
Activated partial thromboplastin time (s)	1 (3.8)	1 (7.1)	0	0	2 (2.5)
Grade 3	1 (3.8)	0	0	0	1 (1.2)
Grade 4	0	1 (7.1)	0	0	1 (1.2)
Glucose (mg/dL) — hyper	1 (3.8)	0	0	0	1 (1.2)
Grade 3	1 (3.8)	0	0	0	1 (1.2)
Grade 4	0	0	0	0	0
Leukocytes (10^3/μL) — hyper	1 (3.8)	0	1 (6.7)	2 (7.7)	4 (4.9)
Grade 3	1 (3.8)	**0**	1 (6.7)	2 (7.7)	4 (4.9)
Grade 4	0	0	0	0	0
Prothrombin international normalized ratio	1 (3.8)	0	0	1 (3.8)	2 (2.5)
Grade 3	1 (3.8)	0	0	1 (3.8)	2 (2.5)
Grade 4	0	0	0	0	0

Data are presented as n (%).

REFERENCES

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