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Hereditary angioedema outcomes in US patients switched from injectable long-term prophylactic medication to oral berotralstat

Marc A. Riedl, MD, MS[*]; Daniel Soteres, MD[†]; J. Wesley Sublett, MD[‡]; Bhavisha Desai, PharmD[§,1]; Dianne Tomita, MPH[§]; Phil Collis, PhD[§]; Jonathan A. Bernstein, MD[¶,‖]; On Behalf of the APeX-S Study Investigators

[*] Division of Rheumatology, Allergy and Immunology, Department of Medicine, University of California San Diego, La Jolla, California
[†] Asthma & Allergy Associates P.C., Colorado Springs, Colorado
[‡] Family Allergy & Asthma, Louisville, Kentucky
[§] BioCryst Pharmaceuticals, Inc, Durham, North Carolina
[¶] University of Cincinnati College of Medicine, Cincinnati, Ohio
[‖] University of Cincinnati, Department of Internal Medicine, Division of Rheumatology, Allergy and Immunology

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ABSTRACT

Background: Berotralstat, a first-line, once-daily, oral plasma kallikrein inhibitor for long-term prophylaxis of hereditary angioedema (HAE), is an effective and well-tolerated treatment option.
Objective: To summarize the safety, effectiveness, and impact on treatment satisfaction in patients who switched from injectable long-term prophylactics to oral berotralstat monotherapy (150 mg daily) at US sites in the international open-label APeX-S study.
Methods: APeX-S was an open-label, Phase II study of berotralstat conducted in 22 countries. Here, we focus on APeX-S patients enrolled at US sites who switched from injectable long-term prophylactics to berotralstat 150 mg once-daily monotherapy.
Results: A total of 34 patients discontinued lanadelumab (n = 21), subcutaneous C1 esterase inhibitor (n = 11), or intravenous C1 esterase inhibitor (n = 2) and switched to berotralstat 150 mg monotherapy. Vomiting, diarrhea, and upper respiratory tract infection were the most common adverse events (each 11.8%). Mean monthly attack rates were consistently low after the switch to berotralstat. The mean (SEM) monthly attack rate was 0.29 (0.11) at Month 1, 0.48 (0.15) at Month 6, and 0.58 (0.23) at Month 12. The median attack rate was 0 attack/mo throughout 12 months of treatment. Improvements were observed in the Treatment Satisfaction Questionnaire for Medication from baseline to Month 12 after the switch to berotralstat monotherapy, with the greatest improvements in convenience.
Conclusion: The transition from injectable prophylactic medication to berotralstat was generally well tolerated. Patients switching to berotralstat monotherapy maintained good control of their HAE symptoms and reported improved treatment satisfaction.
Trial Registration: ClinicalTrials.gov Identifier: NCT03472040.
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Introduction

Hereditary angioedema (HAE) is a rare, debilitating genetic disorder characterized by unpredictable, potentially life-threatening recurrent episodes of swelling (primarily affecting the extremities, upper airway, face, genitals, and abdomen) and is estimated to affect 1 in 50,000 individuals worldwide.[1-3] The most frequently identified cause of HAE is mutations in the C1 esterase inhibitor (C1-INH) gene (serpin family G member 1; *SERPING1*) which lead to either deficient levels of the C1-INH protein (type 1 HAE) or the production of normal levels of dysfunctional C1-INH protein (type 2 HAE).[1,4] C1-INH protein deficiency or dysfunction disrupts regulation of the kallikrein–bradykinin cascade, leading to an increase in bradykinin production, which causes episodes of vascular permeability and swelling.[4]

Current approaches to HAE treatment encompass on-demand acute therapy administered at attack onset and long-term prophylaxis to reduce the frequency and severity of attacks.[1,5] Despite the availability of injectable or infusion-based first-line on-demand (subcutaneous ecallantide, subcutaneous icatibant, and intravenous C1-INH infusion concentrate) and long-term prophylactic (LTP; intravenous or subcutaneous C1-INH, and subcutaneous lanadelumab) treatments, many patients with HAE still experience significant

[1] Previous employee.

Address correspondence to: Jonathan A. Bernstein, MD, University of Cincinnati College of Medicine, Department of Internal Medicine, 231 Albert Sabin Way, ML#563, Cincinnati, OH 45267. E-mail: bernstja@ucmail.uc.edu.

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physical, emotional, and economic burden of the disease with reduced quality of life (QoL).[1,6-8]

Berotralstat, a once-daily, oral plasma kallikrein inhibitor, was approved in several countries for routine prevention of HAE attacks in patients aged ≥12 years and is now recommended for first-line long-term prophylaxis in the 2021 international World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines for the management of HAE.[5,9,10] The availability of a new oral prophylactic treatment opens the door to important discussions about patient preference, including factors such as lifestyle and reasons behind any perceived hesitation toward injectable treatments.[11] Recent surveys of patients diagnosed with HAE indicate that most users of long-term prophylactic therapy, despite liking their current medication, would prefer an oral treatment option because it would better fit their lifestyle and alleviate the burden of treatment associated with an injectable therapy.[6,12]

The efficacy and safety of berotralstat were demonstrated in APeX-2, a Phase III, double-blind, placebo-controlled, international study in which median attack rates decreased over time in patients with type 1 or type 2 HAE who completed 96 weeks of treatment with berotralstat 150 mg (n = 21).[13] In addition, berotralstat was generally well tolerated, and no drug-related treatment-emergent serious adverse events (TESAEs) were reported.[13-15] The long-term safety, effectiveness, and impact on QoL of berotralstat in patients with type 1 or type 2 HAE were further investigated in the international open-label APeX-S trial (NCT03472040).[16,17] Here, we report on the safety, effectiveness, and impact on treatment satisfaction over 12 months in APeX-S patients who switched from prior injectable prophylactic therapy to berotralstat monotherapy (150 mg once daily [QD]) at US sites.

Methods

Study Design and Participants

APeX-S (NCT03472040) was an open-label, Phase II study of berotralstat conducted in 22 countries. The complete methodology for the APeX-S study has been published previously.[16] In brief, eligible patients aged ≥12 years with a clinical diagnosis of type 1 or type 2 HAE were centrally allocated to receive either berotralstat 110 mg or 150 mg once daily until results from the APeX-2 study demonstrated superior efficacy for the 150 mg dose.[13-15] At this point, patients receiving the 110 mg dose were switched to the 150 mg dose, and all subsequently enrolled patients received the 150 mg dose.

Here, we focus specifically on APeX-S patients enrolled at US sites who switched from an injectable LTP to berotralstat 150 mg once daily monotherapy (Fig 1). Patients from non-US sites were not included in this analysis because of variability in injectable LTP restrictions for use in ex-US countries. All enrolled patients in the United States were started on berotralstat 150 mg. US enrollment began on April 30, 2019, and the last US patient exited the study on March 25, 2021, following Food and Drug Administration approval of berotralstat in December 2020.[10] Per protocol, patients enrolled at US sites were eligible to receive berotralstat for up to 96 weeks or until it became commercially available. Due to the Food and Drug Administration approval of berotralstat in December 2020, some patients in the United States switched to commercial berotralstat and did not complete an entire 12 months of dosing on the study. As per the APeX-S study protocol, patients were not required to discontinue and wash out their previous injectable prophylactic treatment before enrollment. Study investigators were encouraged to assess berotralstat response with patients and discontinue concomitant injectable LTPs as appropriate.

APeX-S was designed, performed, and monitored in accordance with Good Clinical Practice guidelines according to the International Council for Harmonisation and in compliance with the Declaration of Helsinki. The protocol, amendments, written informed consent forms, and other relevant study documentation were approved by institutional review boards and independent ethics committees before implementation, in accordance with regulatory requirements.

Objectives and Outcome Measures

The primary objective of APeX-S was to explore the long-term safety and tolerability of daily dosing of oral berotralstat. As secondary objectives, the effectiveness of berotralstat and its impact on QoL and patient satisfaction were evaluated. Patients recorded information on their HAE attack rates in a daily journal, which was confirmed using a programmed algorithm according to criteria predefined in the statistical analysis plan. Attack rate data for patients who received concomitant injectable LTPs with berotralstat were adjusted so that attack rates started at Month 1 of berotralstat monotherapy (ie, attack rates while on concomitant injectable LTPs are not reported here). Adjusted attack rates are defined as the total number of adjusted HAE attacks experienced in the period of interest, adjusted for the length of a month (28 days) and the number of days during that period. The attack must have had a duration of more than 24 hours if untreated and have included at least 1 symptom of swelling and been unique (attack begins >24 hours from the end of the prior attack). Due to the APeX-S study design, investigator-confirmed attack rates were not collected at baseline. Patient satisfaction was assessed over time from baseline using the Treatment Satisfaction Questionnaire for Medication (TSQM).[18] TSQM data are not presented according to month of berotralstat monotherapy because baseline for TSQM was defined as the last nonmissing value (ie, the most recent LTP) before the initiation of berotralstat. It is based on the patient's reflection on their last treatment received. The TSQM consists of 14 items split across 4 domains (global satisfaction, convenience, effectiveness, and adverse effects). The TSQM scale ranges from 0 to 100, with higher scores indicating greater satisfaction.

Statistical Analysis

For this post hoc analysis, descriptive statistics were generated for the full set of US-based patients. From the final data analysis

Figure 1. APeX-S study design. LTP, long-term prophylactic; QD, once daily.

Table 1
Patient Baseline Demographics

Characteristic	Berotralstat 150 mg (N = 34)
Age (y), mean (SD)	38 (17.4)
Female, n (%)	22 (64.7)
Race, n (%)	
Black or African American	1 (2.9)
White	33 (97.1)
Injectable LTP before switch to berotralstat, n (%)	
Lanadelumab	21 (61.8)
Every 2 wk	14 (66.7)
Every 4 wk	4 (19.0)
Other[a]	3 (14.3)
IV C1-INH	2 (5.9)
SC C1-INH	11 (32.4)
History of prior laryngeal attack,[b] n (%)	3 (8.8)

Abbreviations: C1-INH, C1 esterase inhibitor; IV, intravenous; LTP, long-term prophylactic; SC, subcutaneous.
[a]Other lanadelumab dosing: every 3 weeks (n = 1), every 6 weeks (n = 1), and twice a week (n = 1).
[b]Each patient was asked "Have you had a prior laryngeal attack?" before enrolling into APeX-S.

(database locked June 8, 2022), a subset was identified based on prior injectable prophylactic therapy (lanadelumab or C1-INH) for HAE attack rate and TSQM scores. Changes in TSQM scores were calculated from baseline while patients were on prior LTP. To maximize the total number of patients, data from patients receiving intravenous C1-INH (n = 2) were included in the total switch group. However, these data are not presented separately for HAE attack rate and TSQM scores because of the low number of patients.

Means, standard deviations (SDs), standard error of means (SEMs), medians, and ranges (minimum and maximum) were generated for continuous end points (e.g., HAE attack rates). The frequency distribution and associated percentages were calculated for categorical variables (eg, AEs). Where provided, confidence intervals (CIs) based on the signed-rank test are for descriptive purposes only and should not be interpreted in the context of testing a prespecified hypothesis.

No inferential statistics were provided because hypothesis testing for this analysis was not prespecified in the protocol. Descriptive analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, North Carolina), and AE data were coded using the Medical Dictionary for Regulatory Activities version 19.1.

Results

Baseline Demographics

In total, 34 patients discontinued their prior injectable LTP and switched to berotralstat 150 mg monotherapy. Most patients were female (64.7%) and White (97.1%), and the mean (SD) age was 38 (17.4) years (Table 1). The most common injectable LTP taken before berotralstat was lanadelumab, followed by subcutaneous C1-INH and intravenous C1-INH (Table 1). The most common dosing schedules for lanadelumab taken before berotralstat were every 2 and every 4 weeks, which occurred in 14 and 4 of the 21 patients who switched from lanadelumab to berotralstat, respectively. Of the 34 patients who discontinued their prior injectable LTP, 8 (23.5%) discontinued their prior LTP before study drug enrollment and 26 (76.5%) discontinued their prior LTP after initiating treatment with berotralstat. Patients discontinued their prior injectable LTP at a median (range) of 12 (1–49) days before initiation of berotralstat or a median (range) of 23 (1–221) days after initiation of berotralstat.

Safety and Tolerability

Exposure to Berotralstat

The mean (SEM) and median exposure to berotralstat were 321 (22.8) days and 336 days, respectively.

Adverse Events

The switch from injectable LTPs to berotralstat was generally well tolerated. Treatment-emergent adverse events (TEAEs) were reported in 24 of 34 patients (70.6%), including 17 of 21 patients (81.0%) who switched from lanadelumab and 6 of 11 patients (54.5%) who switched from subcutaneous C1-INH (Table 2). The most common TEAEs (in ≥5% of patients) were vomiting, diarrhea, and upper respiratory tract infection, all reported in 4 patients (11.8%) (Table 3). Drug-related TEAEs occurred in 10 of 34 patients (29.4%). No TESAEs were reported in any patient, and none of the patients in this analysis discontinued berotralstat because of a TEAE (Table 2). One patient (2.9%) reported 3 grade 3 TEAEs, none of which were drug-related.

Gastrointestinal (GI) TEAEs were mild or moderate and reported in 12 of 34 patients (35.3%), 8 (23.5%) of which were considered related to the study drug. GI TEAEs were reported in 8 of 21 patients (38.1%) who switched from lanadelumab, 3 of 11 patients (27.3%) who switched from subcutaneous C1-INH, and 1 of 2 patients (50.0%) who switched from intravenous C1-INH.

Effectiveness

Hereditary Angioedema Attack Rates

Individual monthly patient attack rates recorded during berotralstat monotherapy are found in eFigure 1; most patients had consistently low monthly HAE attack rates.

Mean monthly attack rates for all 34 patients were consistently low during berotralstat monotherapy after the switch from the previous

Table 2
Summary of TEAEs in Patients Who Switched to Berotralstat Monotherapy From a Previous Injectable LTP

	Berotralstat 150 mg, n (%)			
	Lanadelumab (n = 21)	SC C1-INH (n = 11)	IV C1-INH (n = 2)	Total (N = 34)
Any TEAE	17 (81.0)	6 (54.5)	1 (50.0)	24 (70.6)
Any drug-related TEAE	7 (33.3)	2 (18.2)	1 (50.0)	10 (29.4)
Any TESAE	0	0	0	0
Any drug-related TESAE	0	0	0	0
Any grade 3 or 4 TEAE	1 (4.8)	0	0	1 (2.9)
Any drug-related grade 3 or 4 TEAE	0	0	0	0
Any TEAE leading to interruption of study drug	1 (4.8)	1 (9.1)	0	2 (5.9)
Any TEAE leading to discontinuation of study drug	0	0	0	0
Any investigator-identified rash	0	0	0	0
Any GI abdominal-related TEAE	8 (38.1)	3 (27.3)	1 (50.0)	12 (35.3)
Any GI abdominal-related TEAE leading to discontinuation	0	0	0	0

Abbreviations: C1-INH, C1 esterase inhibitor; GI, gastrointestinal; IV, intravenous; LTP, long-term prophylactic; SC, subcutaneous; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Table 3
TEAEs Occurring in ≥5% of Patients

TEAE, n (%)	Berotralstat 150 mg (N = 34)
Vomiting	4 (11.8)
Diarrhea	4 (11.8)
Upper respiratory tract infection	4 (11.8)
Nausea	3 (8.8)
Insomnia	3 (8.8)
Pharyngitis	2 (5.9)
Abdominal discomfort	2 (5.9)
Back pain	2 (5.9)
Dysmenorrhea	2 (5.9)

Abbreviation: TEAE, treatment-emergent adverse event.

injectable LTP (Fig 2). The mean (SEM) monthly attack rate was 0.29 (0.11) at Month 1, 0.48 (0.15) at Month 6, and 0.58 (0.23) at Month 12. Median attack rates remained at 0 per month through 12 months of berotralstat monotherapy after the switch from injectable LTPs.

In patients who switched from lanadelumab to berotralstat monotherapy (Fig 2), the mean (SEM) attack rate was 0.14 (0.08) at Month 1 and 0.30 (0.16) at Month 6, which was sustained to Month 12 (0.26 [0.18]). Median attack rates remained at 0 per month to 12 months of berotralstat monotherapy after the switch from lanadelumab.

In patients who switched from subcutaneous C1-INH to berotralstat monotherapy (Fig 2), the mean (SEM) attack rate was 0.55 (0.28) at Month 1, 0.82 (0.33) at Month 6, and 1.18 (0.72) at Month 12. Median attack rates remained at 0 per month for 9 of the 12 months of berotralstat monotherapy after the switch from subcutaneous C1-INH. Notably, one outlier patient in this group (patient 6) had exceptionally high HAE attack rates despite treatment. When this patient's data were removed, the mean attack rates in the subcutaneous C1-INH group were comparable with that of the total group. Because of the low overall number of patients in this study, it was decided that this patient's data would not be removed.

Overall, patients remained attack-free for 96.6% of the days on berotralstat monotherapy. After switching from lanadelumab or subcutaneous C1-INH to berotralstat monotherapy, patients remained attack free for 98.0% and 94.3% of the days overall, respectively. Patients remained attack free for 97.1% of the days during Month 1 of berotralstat monotherapy, which was sustained to Month 6 (96.3%) and Month 12 (95.9%). The maximum and average (SEM) duration of attack-free days on berotralstat monotherapy were 221.0 (21.19) and 155.5 (21.01) days, respectively. In patients who switched from lanadelumab to berotralstat monotherapy, the maximum and average (SEM) duration of attack-free days were 241.6 (25.48) and 173.8 (25.18) days, respectively. In patients who switched from subcutaneous C1-INH to berotralstat monotherapy, the maximum and average (SEM) duration of attack-free days were 184.7 (43.16) and 136.2 (42.59) days, respectively.

Use of on-demand medication for all 34 patients declined from 20.6% at Month 1 to 14.3% at Month 12. During the same period, a reduction in the use of on-demand medication from 14.3% to 7.7% and 27.3% to 16.7% was observed in patients who switched to berotralstat monotherapy from lanadelumab and subcutaneous C1-INH, respectively.

Treatment Satisfaction Scores

Overall, TSQM scores improved in patients who switched to berotralstat monotherapy, with the greatest change (mean [95% CI]) from baseline to Month 12 (mean [SEM]) observed in the convenience (35.35 [95% CI, 23.30-47.41] change; 61.27 [3.92] at baseline; 93.69 [2.01] at Month 12) and global satisfaction (19.16 [95% CI, 7.78-30.53] change; 69.33 [4.38] at baseline; 87.34 [4.12] at Month 12) domains (Fig 3A). Effectiveness and side effect scores remained fairly consistent from baseline to Month 12 (Fig 3A).

A similar trend was observed in patients who switched from lanadelumab to berotralstat monotherapy (Fig 3B), with improvements (mean [95% CI]) from baseline to Month 12 (mean [SEM]) in patient-reported convenience (26.07 [95% CI, 10.66–41.47] change; 69.84 [4.53] at baseline; 94.87 [2.04] at Month 12) and global satisfaction (15.38 [95% CI, −1.41 to 32.18] change; 71.77 [6.11] at baseline; 90.11 [3.92] at Month 12) scores.

In patients who switched from subcutaneous C1-INH to berotralstat (Fig 3C), improvements (mean [95% CI]) from baseline to Month

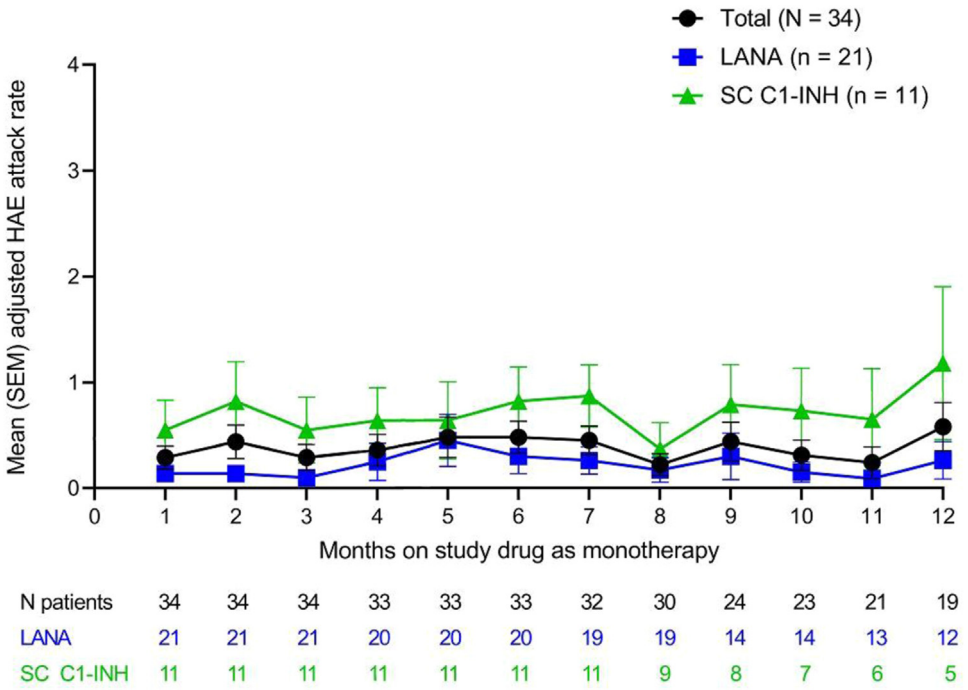

Figure 2. Mean adjusted monthly HAE attack rates during berotralstat monotherapy after switch from previous long-term prophylactic. C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; LANA, lanadelumab; SC, subcutaneous.

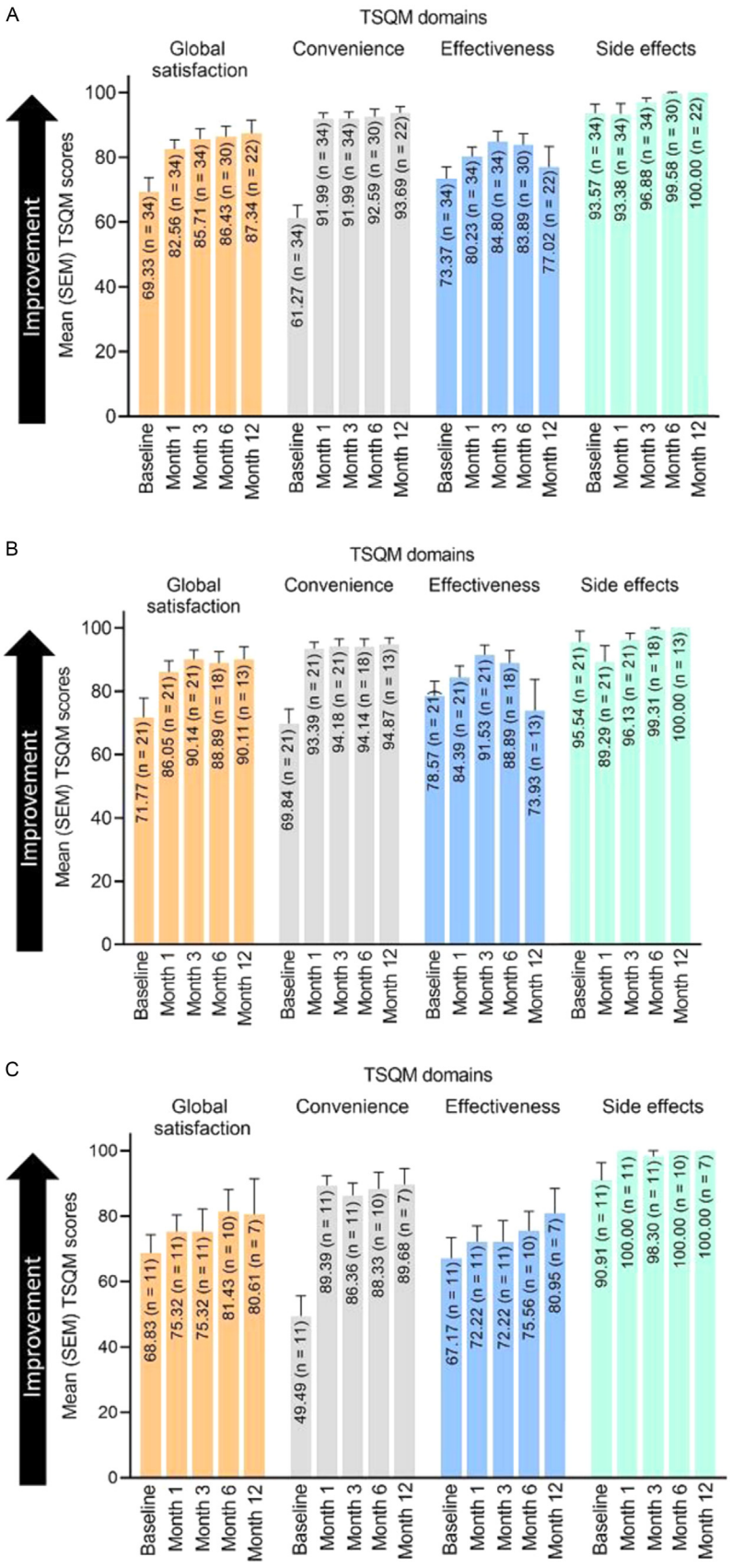

Figure 3. Mean (SEM) TSQM scale scores in (A) all patients who switched to berotralstat; (B) patients who switched from lanadelumab to berotralstat; and (C) patients who switched from SC C1-INH to berotralstat. C1-INH, C1 esterase inhibitor; SC, subcutaneous; TSQM, Treatment Satisfaction Questionnaire for Medication.

12 (mean [SEM]) were observed in patient-reported convenience (44.44 [95% CI, 19.80–69.09] change; 49.49 [6.15] at baseline; 89.68 [4.91] at Month 12), effectiveness (21.43 [95% CI, 1.88–40.98] change; 67.17 [6.29] at baseline; 80.95 [7.46] at Month 12), global satisfaction (18.37 [95% CI, 0.54–36.20] change; 68.83 [5.56] at baseline; 80.61 [10.77] at Month 12), and adverse effects (11.61 [95% CI, −8.54 to 31.75] change; 90.91 [5.42] at baseline; 100.00 [0.00] at Month 12) scores.

Discussion

In this study, we report on the safety, effectiveness, and impact on treatment satisfaction of berotralstat monotherapy (150 mg QD once daily) in US-based APeX-S patients with type 1 or type 2 HAE who switched to berotralstat monotherapy from prior injectable LTPs.

The safety data collected in this analysis are consistent with the safety data previously reported in APeX-2 and APeX-S,[15,16] and indicate that the switch from injectable LTPs to berotralstat was generally well tolerated.

The effectiveness of berotralstat in patients who switched from previous injectable LTPs to berotralstat was consistent with effectiveness data from the overall APeX-S population.[16] That is, HAE symptoms remained well controlled for most patients in this analysis during the treatment switch process.

Treatment satisfaction improved in patients who switched from prior injectable LTPs to berotralstat monotherapy, with the greatest improvements in convenience and global satisfaction. These data suggest that berotralstat may improve the overall experience of patients taking LTP for HAE. Moreover, the consistent effectiveness and adverse effects scores from baseline to Month 12 demonstrate that patients perceived berotralstat to be as effective and tolerable as their prior LTP.

In a survey of 75 US-based patients diagnosed with having type 1 or type 2 HAE, 64% reported the use of injectable or androgen HAE prophylactics.[6] Although patients agreed with the importance of taking preventive medication, 57% considered prophylactic treatment to be burdensome.[6] Of the 48 patients on prophylaxis, 98% indicated that they liked their current preventive medication but would prefer an oral treatment if one was available.[6] Our findings are in accordance with this survey, as we found improvements in overall treatment satisfaction and convenience following the switch from injectable LTPs to oral berotralstat monotherapy.

In clinical practice, patients may switch from injectable prophylactics to berotralstat through a variety of methods, such as abrupt discontinuation, tapering, or overlapping the injectable prophylactic with berotralstat. In the APeX-S clinical trial, this latter method was recommended for patients transitioning from lanadelumab or C1-INH. Importantly, the method used should be individualized based on physician and patient preferences and characteristics. Patients who were enrolled in the APeX-S study and transitioned from injectable prophylactics to berotralstat while overlapping therapies were described in 2 recent case reports.[19,20] One described 2 familial patients who successfully transitioned from SC and intravenous C1-INH without tapering,[19] and the other described 3 patients who successfully transitioned from lanadelumab with tapering.[20] In this study, patients switched through a variety of methods. For example, some patients abruptly discontinued their injectable therapy when initiating berotralstat, while others overlapped with berotralstat before stopping their injectable therapy.

The data presented here on berotralstat monotherapy are not intended (or suitable) for comparing patients who switched from lanadelumab to berotralstat with those who switched from subcutaneous C1-INH to berotralstat. These therapies are known to have different half-lives. It has been found in Phase Ia and Ib studies that, depending on the dose, lanadelumab has an elimination half-life ranging from 13.8 to 21.2 days[21-24]; therefore, it could continue to prevent HAE symptoms after the switch to berotralstat. In contrast, intravenous and subcutaneous recombinant and plasma-derived C1-INH therapies have much shorter elimination half-lives (up to 3 hours depending on dose for conestat alfa [recombinant C1-INH concentrate]; up to 62 hours for intravenous human pasteurized C1-INH concentrate; and up to 120 hours for SC human pasteurized C1-INH concentrate).[5,25-27]

This study has several limitations. First, investigator-confirmed baseline attack rates were not collected for APeX-S patients. APeX-S was an open-label study and was therefore designed primarily to evaluate safety rather than efficacy. Another limitation was the small patient population (n = 34) and the small number of patients switching from intravenous C1-INH (n = 2). As noted previously, the residual preventive effects after the discontinuation of prior LTPs used during the study must be considered, particularly in patients treated with lanadelumab (which has a long half-life). Notably, a few patients experienced increased HAE attacks (3 to 4 in some months) during the berotralstat monotherapy treatment period, including lanadelumab patients 7 and 9 and subcutaneous C1-INH patients 6 and 7 (eFig 1). As a full history of HAE attacks before the administration of any treatment was not collected as part of the APeX-S study protocol, it is difficult to assess whether these patients had a more severe disease profile before the study enrollment.[16] These data suggest that most patients maintain low attack rates on berotralstat monotherapy, but additional research is needed to support these findings. Finally, our study outcomes may have been affected by selection bias. The patients enrolled in this study were willing to discontinue their pre-existing LTP treatment for berotralstat. Despite some level of satisfaction with their previous LTP (as indicated by TSQM scores at baseline), increases in TSQM scores from baseline during this study may indicate that patients were not completely satisfied with their prior LTP. As such, the patients in this study may not necessarily generalize to the entire population of LTP users in the US.

Taken together, our findings highlight the importance of adopting an individualized approach to HAE treatment that considers efficacy and safety, including the potential benefits of presenting patients with a variety of treatment options with different routes of administration and dosing schedules. This approach may positively affect treatment adherence and satisfaction, leading to improved QoL.[6,11,28] Indeed, berotralstat as a once-daily, orally administered LTP may offer patients a convenient treatment option for improved adherence and long-term effectiveness.

US-based APeX-S patients diagnosed with type 1 or type 2 HAE who switched from injectable LTPs to berotralstat monotherapy (150 mg QD once daily) experienced no new safety signals and had consistently low attack rates while on monotherapy. Patients remained attack free for 96.6% of the days. Improvements in treatment satisfaction were also observed in these patients, with effectiveness scores remaining consistently high from baseline to Month 12. Our findings support the importance of adopting an individualized approach to HAE treatment and highlight the patient-perceived benefits of an oral LTP.

Ethics Approval

The APeX-S study was designed, performed, and monitored in accordance with Good Clinical Practice guidelines according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and in compliance with the Declaration of Helsinki. The protocol, amendments, informed consent forms, and other relevant study documentation were approved by institutional review boards and independent ethics committees before implementation, in accordance with regulatory requirements.

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Disclosures

Dr Riedl is a research investigator and/or consultant for Astria Therapeutics, BioCryst Pharmaceuticals, BioMarin Pharmaceutical, CSL Behring, Cycle Pharmaceuticals, Fresenius Kabi, Ionis Pharmaceuticals, Ipsen, KalVista Pharmaceuticals, Ono Pharmaceutical, Pfizer, Pharming, Pharvaris, REGENXBIO, and Takeda; he has provided speaker presentations for CSL Behring, Pharming, and Takeda.

Dr Soteres is a research investigator for BioCryst Pharmaceuticals, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharvaris, and Takeda; he is a speaker and/or consultant for BioCryst Pharmaceuticals, CSL Behring, Cycle Pharma, KalVista Pharmaceuticals, and Takeda.

Dr Sublett has contracted research for Aimmune, ALK-Abello, AstraZeneca, BioCryst Pharmaceuticals, Evidera, GlaxoSmithKline, LEO Pharma, Novartis, Octapharma, Regeneron Pharmaceuticals, Sanofi, and Teva Pharmaceuticals; he is a consultant for Bryn Pharma, Optinose, Pfizer, Regeneron Pharmaceuticals, and Sanofi; he is a speaker for Amgen, AstraZeneca, Regeneron Pharmaceuticals, and Sanofi.

Dr Desai, Ms Tomita, and Dr Collis are employees of and own stock in BioCryst Pharmaceuticals.

Dr Bernstein is a principal investigator, consultant, and speaker for BioCryst Pharmaceuticals, CSL Behring, Pharming, and Takeda/Shire; he is a principal investigator and consultant for BioMarin Pharmaceutical, Intellia Therapeutics, Ionis Pharmaceuticals, KalVista Pharmaceuticals, and Pharvaris.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2023.11.016.

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Supplementary Data

Previous prophylaxis	Months 1	2	3	4	5	6	7	8	9	10	11	12
LANA 1	0	0	0	0	0	0	1	1	0	0	0	0
LANA 2	0	0	0	0	1	0	1	0	1	0	0	2
LANA 3	1	0	0	0	1	0	1	0	0	0	0	0
LANA 4	0	1	0	0	0	0	0	0	0	0	0	0
LANA 5^	1	0	1	0	0	1	0	0				
LANA 6	0	0	0	0	0	1	0	0	0	0	0	0
LANA 7^	0	0	1	3	4	3						
LANA 8	0	0	0	0	0	0	0	0	0	0	0	0
LANA 9	1	0	0	2	3	0	2	2	3	0	1	1
LANA 10	0	0	0	0	0	0	0	0	0	1	0	0
LANA 11^	0	0	0	0	0	0	0	0				
LANA 12^	0	0	0	0	0	0	0	0	0	0		
LANA 13	0	1	0	0	0	1	0	0	0	0	0	0
LANA 14	0	0	0	0	0	0	0	0	0	1	0	0
LANA 15	0	0	0	0	0	0	0	0	0	0	0	0
LANA 16	0	0	0	0	0	0	0	0	0	0	0	0
LANA 17^	0	0	0	0	0	0	0					
LANA 18^	0	0	0	0	0	0	0					
LANA 19^	0	0	0	0	0	0	0					
LANA 20^	0	0	0									
LANA 21^	0	1	0	0	0	0	0	0	0	0	0	
SC C1-INH 1	2	1	0	0	0	1	1	0	0	1	0	0
SC C1-INH 2*	0	1	0	2	1	2	1	1	1	1	1	
SC C1-INH 3^	0	0	0	0	1	0	0	0				
SC C1-INH 4^	0	0	0	0	0	0	1					
SC C1-INH 5†	0	0	1	0	0	0	0	0	0	0		
SC C1-INH 6	2	4	3	3	4	3	2	2	3	3	3	3
SC C1-INH 7	2	1	2	1	1	2	3	0	1	0	0	3
SC C1-INH 8	0	0	0	0	0	0	0	0	0	0	0	0
SC C1-INH 9	0	2	0	1	0	1	1	0	1	0	0	0
SC C1-INH 10^	0	0	0	0	0	0	0	0	0			
SC C1-INH 11^	0	0	0	0	0	0	0					
IV C1-INH 1	0	0	0	0	0	1	0	0	0	0	0	1
IV C1-INH 2	1	3	2	0	0	0	0	0	0	0	0	1
	Number of HAE attacks											
Key												
	0	1	2	3	4							

C1-INH, C1 esterase inhibitor; *IV*, intravenous; *LANA*, lanadelumab; *SC*, subcutaneous.

eFigure 1. Individual monthly patient HAE attack rates during berotralstat monotherapy after switch from previous long-term prophylactic (N = 34). Discontinuation of berotralstat before Month 12 due to *perceived lack of efficacy, †patient noncompliance, or ^berotralstat being available through another mechanism. C1-INH, C1 esterase inhibitor; IV, intravenous; LANA, lanadelumab; SC, subcutaneous.