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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria, and Skin Disease

Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial

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Abstract

Background: With no approved treatments in Japan for the prevention of hereditary angioedema (HAE) attacks, there is a significant unmet need for long-term prophylactic therapies for Japanese patients with HAE. Berotralstat (BCX7353) is an oral, once-daily, highly selective inhibitor of plasma kallikrein in development for prophylaxis of angioedema attacks in HAE patients.

Methods: APeX-J is a phase 3, randomized, double-blind, placebo-controlled, parallel-group, 3-part trial conducted in Japan (University Hospital Medical Information Network identifier, UMIN000034869; ClinicalTrials.gov identifier, NCT03873116). Patients with a clinical diagnosis of type 1 or 2 HAE underwent a prospective run-in period of 56 days to determine eligibility, allowing enrollment of those with ≥2 expert-confirmed angioedema attacks. Patients were randomly assigned (1:1:1) and stratified by baseline attack rate (≥2 vs. <2 expert-confirmed attacks/month between screening and randomization) to receive once-daily berotralstat 110 mg, berotralstat 150 mg, or placebo. The primary endpoint was the rate of expert-confirmed angioedema attacks during dosing in the 24-week treatment period.

Results: Nineteen patients were randomized to receive once-daily berotralstat 110 mg (n = 6), berotralstat 150 mg (n = 7), or placebo (n = 6). Treatment with berotralstat 150 mg significantly reduced HAE attacks relative to placebo (1.11 vs. 2.18 attacks/month, p = .003). The most frequently reported treatment-emergent adverse events (TEAEs) in berotralstat-treated patients (n = 13) were nasopharyngitis (n = 4, 31%), abdominal pain, cough, diarrhea, and pyrexia (n = 2 each, 15%).

Abbreviations: HAE, hereditary angioedema.

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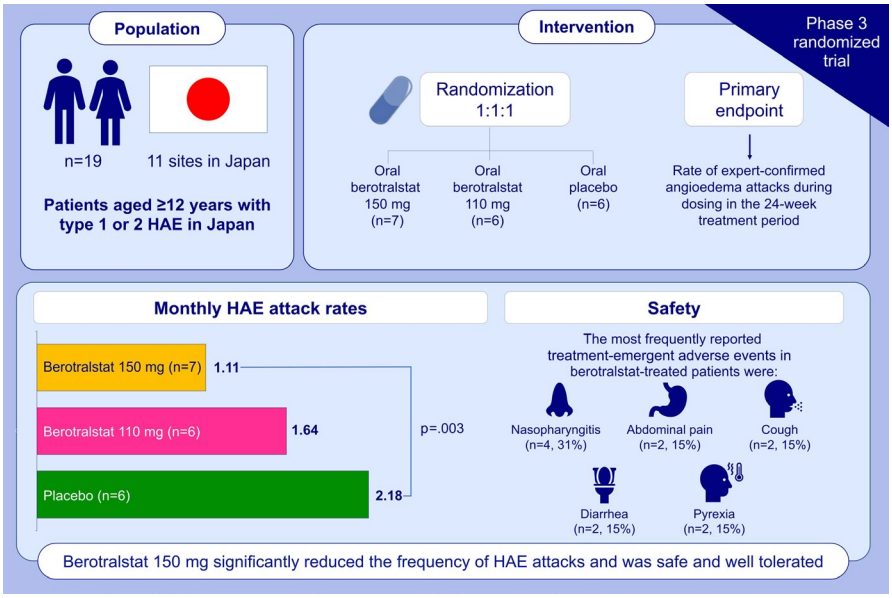
Conclusions: Orally administered, once-daily berotralstat 150 mg significantly reduced the frequency of HAE attacks and was safe and well tolerated, supporting its use as a prophylactic therapy in patients with type 1 or 2 HAE in Japan.

KEYWORDS
berotralstat, hereditary angioedema, Japan, kallikrein inhibitor, prophylaxis



GRAPHICAL ABSTRACT
APeX-J is a phase 3, placebo-controlled trial conducted in Japan to assess the efficacy and safety of oral berotralstat in patients with HAE. Patients were randomized 1:1:1 to receive once-daily berotralstat 110 mg, berotralstat 150 mg, or placebo. Berotralstat 150 mg significantly reduced the frequency of HAE attacks compared with placebo, supporting its use as a prophylactic therapy.

1 | INTRODUCTION

Hereditary angioedema (HAE) is a rare, chronic disease characterized by unpredictable, recurrent angioedema attacks primarily mediated by uncontrolled plasma kallikrein activity and overproduction of bradykinin.[1,2] Excess bradykinin leads to vasodilation, vascular leakage, and consequent swelling.[2,3] HAE attacks most commonly affect the extremities, face, abdomen, and larynx.[4] Although less frequent, laryngeal attacks are potentially life-threatening because of the risk of rapid onset of respiratory obstruction and asphyxiation.[5] For this reason, international guidelines recommend that all patients should have access to on-demand medication for treatment of acute attacks.[6–8] The clinical manifestations of HAE and the unpredictability of attacks can result in significant physical, emotional, and economic burdens for patients and families, including higher levels of anxiety and depression, inability to perform daily activities, and high direct and indirect care costs.[9–12] Therefore, it is important that management of HAE focuses on reducing the frequency and severity of future attacks with prophylactic treatment in addition to on-demand therapies.[6,13]

While prophylactic treatment options, including intravenous (IV) or subcutaneous (SC) formulations of C1-esterase inhibitor (C1-INH) replacement therapy and a SC plasma kallikrein inhibitor,[14] are available to prevent HAE attacks in the United States and Europe, none of these therapies are currently approved for long-term prophylaxis in Japan.

In Japan, HAE is estimated to affect 2500 patients, and the recognition of HAE by physicians is low.[15–17] Further, only 2 on-demand therapies are currently approved by the Japanese Ministry of Health, Labour and Welfare (MHLW) for the treatment of acute HAE attacks—IV plasma-derived C1-INH and SC icatibant—and only icatibant is approved for self-administration.[18,19] If the angioedema attack worsens after self-administration of icatibant, patients must visit their healthcare providers to receive plasma-derived C1-INH, and patients often live in fear that they will not arrive in time to the hospital or clinic. Additionally, the number of hospitals where HAE patients can receive plasma-derived C1-INH is unacceptably low and some prefectures have no medical facilities with disclosed stock of plasma-derived C1-INH.[15,16] Both the 2010 and updated 2014 guidelines for HAE by the Japanese Association

for Complement Research recommend danazol and tranexamic acid for prophylaxis of attacks in patients with a history of laryngeal edema; however, danazol is not approved by the MHLW, and tranexamic acid is indicated for symptoms of erythema, itching, and swelling associated with diseases such as eczema, urticaria, drug eruption, and toxicoderma.[20–23] Therefore, there is an urgent need for targeted prophylactic therapies to reduce the frequency and severity of angioedema attacks for patients in Japan.

Berotralstat (BCX7353) is an oral, highly selective inhibitor of plasma kallikrein in development for prophylaxis of angioedema attacks in patients with HAE, with pharmacological characteristics that support once-daily dosing.[24] The phase 3 APeX-2 trial was designed to assess the efficacy and safety of 2 once-daily doses of berotralstat (110 mg and 150 mg) for prophylaxis of angioedema attacks in patients with HAE in North America and Europe. At the primary analysis (24 weeks of dosing), both doses of berotralstat significantly reduced the frequency of HAE attacks compared with placebo (1.65 attacks/month at 110 mg [$p = .024$] and 1.31 attacks/month at 150 mg [$p < .001$] vs. 2.35 attacks/month with placebo) and were found to be safe and generally well tolerated.[25]

Due to the urgent unmet need for prophylactic therapy in Japan, berotralstat received Sakigake Designation from the MHLW, which accelerates the development of innovative medicines.[26] Herein, we report the primary efficacy and safety results of berotralstat for prophylaxis of HAE attacks from the phase 3 APeX-J trial of patients with type 1 or 2 HAE in Japan.

2 | METHODS

2.1 | Study design

APeX-J (study number BCX7353-301) is an ongoing, phase 3, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 11 sites in Japan, 10 of which randomized patients. Part 1 of the study was a 24-week double-blind evaluation of the efficacy and safety of berotralstat 110 mg and 150 mg for the prophylaxis of HAE attacks compared with placebo. Following completion of 24 weeks of double-blind treatment, patients randomized to placebo were rerandomized 1:1 to berotralstat 110 mg or 150 mg in a double-blind manner (part 2, weeks 25-52) to further evaluate safety and effectiveness. This study remains ongoing and data presented herein summarize the results of the 24-week placebo-controlled period only.

This study was conducted in compliance with the current version of the Japan Pharmaceuticals and Medical Devices Act, Declaration of Helsinki, and current International Council for Harmonisation and Good Clinical Practice guidelines. An independent, program-wide data monitoring committee provided review of safety data at prespecified intervals with additional consultation or review as needed. All patients provided written informed consent. The trial is registered on the UMIN (University Hospital Medical Information Network) Clinical Trials Registry (UMIN identifier, UMIN000034869) and ClinicalTrials.gov (NCT03873116).

2.2 | Patients

Eligible patients were aged ≥12 years with a clinical diagnosis of HAE type 1 or 2, defined as having a C1-INH functional level <50% and a complement 4 (C4) level below the lower limit of normal (LLN) reference range as assessed during the screening period. Patients with a C1-INH functional level between 50% and the assay LLN (74%) or a C4 value above the LLN could qualify via alternative protocol-specified criteria (options for C1-INH: either single-repeat measurement or *SERPING1* mutation known or likely to be pathogenic; options for C4: low C4 during an HAE attack, a physician-confirmed family history of C1-INH deficiency, or *SERPING1* mutation known or likely to be pathogenic). Patients underwent a prospective run-in period of 56 days to determine eligibility. Patients with ≥2 independent expert-confirmed HAE attacks during the prospective run-in period were eligible for enrollment. Enrolled patients were required to have access to ≥1 targeted medication approved by the MHLW (ie, plasma-derived C1-INH or icatibant). Patients were excluded from study if they had used androgens or tranexamic acid for prophylaxis of angioedema attacks within the 28 days before the screening visit or had any planned initiation during study, or had used C1-INH for prophylaxis of angioedema attacks within 14 days before screening or had any planned initiation during study. Prophylaxis was defined as administration of medication in the absence of symptoms of an angioedema attack. Acute use of a C1-INH therapy for the treatment of angioedema attacks was not excluded at any time, nor was the use of C1-INH for preprocedural prophylaxis for an unplanned procedure.

2.3 | Procedures

Eligible patients were randomized 1:1:1 to berotralstat 110 mg, berotralstat 150 mg, or placebo into part 1 of the study via an interactive response system. Randomization was stratified by baseline expert-confirmed attack rate (≥2 attacks/month vs. <2 attacks/month) at time of randomization. Expert-confirmed HAE attacks that occurred between screening and first dose were used to calculate a baseline expert-confirmed attack rate for use in the statistical analysis. Study drug assignment was blinded to the investigator, study staff, patients, and clinical research organization staff. Patients were instructed to take each dose at the same time every day during or within 30 min of eating, typically the largest meal of the day.

Details of angioedema attacks, including time of event, symptoms, anatomical location, severity, and treatments were recorded by the patient in an electronic diary. Within approximately 2 business days of the end of each attack, patients were contacted by the investigator to discuss the attack. An independent expert (an experienced HAE treater in Japan) was selected by the sponsor to review all reported angioedema attacks. The electronic diary and any investigator-collected information were used by the independent expert

to either confirm or reject the attack. Angioedema attacks were treated in accordance with the medical management plan advised by the investigator or treating physician.

Safety was assessed by the collection of adverse events (AEs), laboratory assessments, physician examinations, vital signs, and electrocardiograms throughout the study.

2.4 | Outcomes

The primary efficacy endpoint was the rate of expert-confirmed angioedema attacks during the 24-week dosing period. Secondary endpoints included the number and proportion of days with angioedema symptoms, the rate of expert-confirmed angioedema attacks during dosing in the effective treatment period (steady state, beginning on day 8), and the change from baseline in quality of life at week 24 as assessed by the angioedema quality of life (AE-QoL) questionnaire.[27,28] Exploratory endpoints included the use of on-demand medications to treat angioedema attacks and the proportion of ≥50% responders to study drug. The proportion of ≥70% and ≥90% responders were added as exploratory endpoints in a protocol amendment.

Safety endpoints included treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), grade 3 or 4 TEAEs, grade 3 or 4 laboratory abnormalities, and discontinuations due to TEAEs. TEAEs were defined as AEs that occurred on or after first dose of study treatment. Gastrointestinal (GI) symptoms, primarily mild, have been noted in previous clinical trials.[25,29,30] The Medical Dictionary for Regulatory Activities (MedDRA) v19.1 categories of GI AEs are much broader than the scope of GI AEs observed in clinical trials; therefore, abdominal TEAEs were defined for phase 3 studies as those GI TEAEs with high-level group terms of (1) GI signs and symptoms and (2) GI motility and defecation conditions.

2.5 | Statistical analysis

The sample size considered feasible for enrollment in Japan had limited statistical power. Assuming an angioedema attack rate for placebo patients of 3.6 attacks/month and a common standard deviation of 2.0 attacks/month for berotralstat and placebo, a sample size of 8 patients in each treatment group was anticipated to have 61% power to detect a ≥67% reduction in angioedema attack rate (from 3.6 to 1.2 attacks/month) comparing berotralstat with placebo.

Analyses included all patients randomized to study drug (intent-to-treat population). Comparisons between each berotralstat dose group and placebo in the rate of expert-confirmed angioedema attacks during the entire dosing period were made using a negative binomial regression model. The number of expert-confirmed angioedema attacks was included as the dependent variable, treatment was a fixed effect, baseline monthly angioedema attack rate was a covariate, and the logarithm of duration on treatment was an offset variable. Analysis of the rate of expert-confirmed attacks during the effective dosing period was similarly conducted, as was the number of attacks requiring treatment with on-demand medication. The proportion of days with angioedema symptoms was analyzed using an analysis of covariance model with baseline attack rate as a covariate and treatment included as a fixed effect. Changes from baseline in AE-QoL scores were analyzed using a mixed model for repeated measures with fixed effects for treatment, baseline attack rate, baseline AE-QoL, visit, a visit-by-treatment-interaction effect, and a random effect for patient.

The baseline requirements for expert-confirmed attack rate had 2 additional requirements not applied to the entire dosing period on-study attacks: (1) attacks had to be unique, and (2) require treatment, medical attention, or cause functional impairment. To allow for a more direct comparison of angioedema attack rates occurring during the baseline and dosing periods, the 2 additional requirements for expert-confirmed baseline attacks were applied programmatically

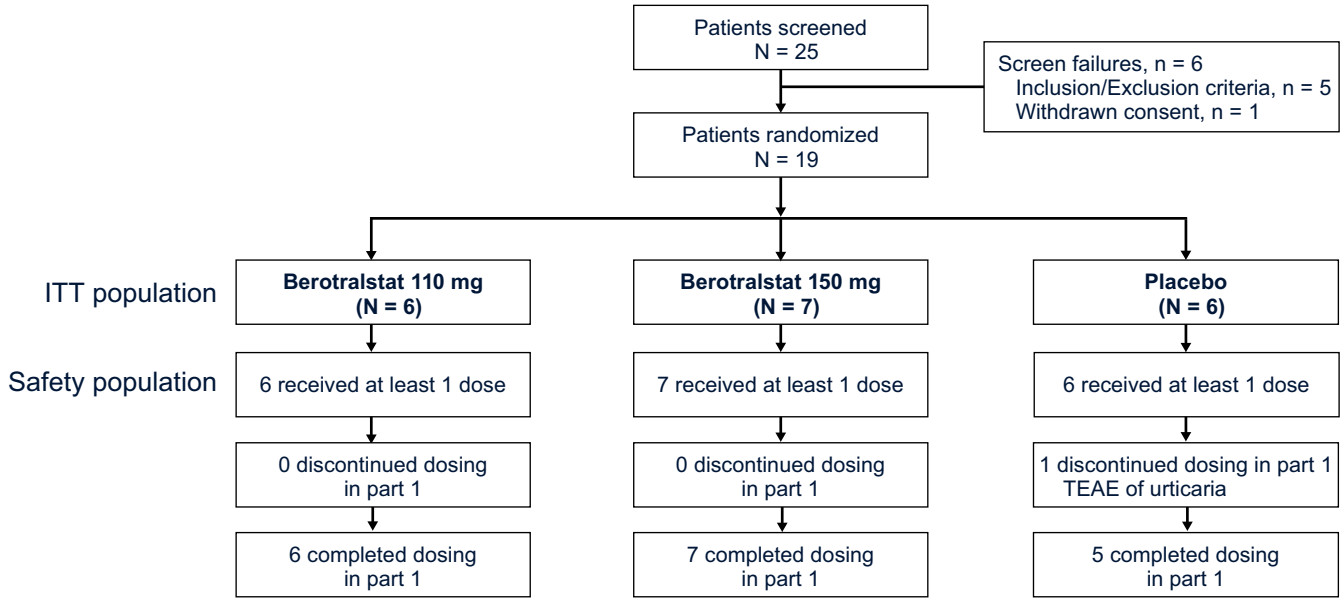


FIGURE 1 APeX-J CONSORT diagram. ITT, intent-to-treat; TEAE, treatment-emergent adverse event

to the on-study expert-confirmed attacks occurring during the dosing period, resulting in an adjusted expert-confirmed attack rate. Adjusted expert-confirmed attack rates were used to compare on-study attack rates to baseline attack rates for the exploratory ≥50%, ≥70%, and ≥90% responder endpoints.

Primary and secondary endpoints were tested hierarchically, with the type 1 error rate controlled at the study level using a combination of hierarchical testing and the Hochberg procedure.[31] For the primary endpoint, the 2 berotralstat doses were tested at the $\alpha = .05$ level, comparing active treatment to placebo. If the maximum of the 2 *p* values was ≤.05, the null hypothesis of no difference between the attack rate for patients on active and placebo treatment was rejected for both doses, and testing proceeded to the next endpoint in the hierarchy with $\alpha = .05$. If the maximum of the 2 *p* values was >.05 but the minimum of the 2 *p* values was <.025, the null hypothesis for the dose with $p < .025$ was rejected, and testing for only that dose proceeded to the next endpoint in the hierarchy with $\alpha = .025$. Otherwise, the null hypothesis for both doses was not rejected and the next endpoint in the hierarchy was not tested. The rate of expert-confirmed angioedema attacks during the 24-week dosing period was the first endpoint in the hierarchy, followed by the number and proportion of days with angioedema symptoms, the rate of expert-confirmed angioedema attacks during dosing in the effective treatment period, and the change from baseline in AE-QoL at week 24.

Safety analyses were performed using the safety population (all patients receiving ≥1 dose of study drug) and are summarized with descriptive statistics.

3 | RESULTS

3.1 | Study population

The study period for the current analysis was December 2018 (first patient enrolled) to November 2019 (24-week visit of the last patient). Of the 25 patients screened, 19 were randomized to receive once-daily berotralstat 110 mg (*N* = 6), berotralstat 150 mg (*N* = 7), or placebo (*N* = 6; Figure 1). Overall, 18 patients (95%) completed dosing through week 24 and one patient in the placebo group discontinued study drug early due to a TEAE of urticaria.

TABLE 1 Baseline characteristics of the intent-to-treat population

Characteristic	Berotralstat 110 mg (*N* = 6)	Berotralstat 150 mg (*N* = 7)	Placebo (*N* = 6)	Total (*N* = 19)
Mean age at time of consent, years (SD)	47 (15)	37 (9)	42 (14)	42 (13)
Sex, *n* (%)				
Male	1 (17)	1 (14)	1 (17)	3 (16)
Female	5 (83)	6 (86)	5 (83)	16 (84)
Race, *n* (%)				
Asian	6 (100)	6 (86)	6 (100)	18 (94)
Other	0	1 (14)	0	1 (5)
Mean weight, kg (SD)	66 (12)	57 (10)	73 (16)	65 (14)
Mean BMI, kg/m^2 (SD)	26 (4)	22 (5)	29 (6)	25 (5)
Mean baseline expert-confirmed angioedema attack rate (SD)[a]	2.4 (1.3)	2.0 (1.1)	2.5 (1.5)	2.3 (1.2)
Categorized baseline expert-confirmed angioedema attack rate, *n* (%)				
≥2 attacks/month	2 (33)	4 (57)	3 (50)	9 (48)
<2 attacks/month	4 (67)	3 (43)	3 (50)	10 (53)
Any past prophylactic treatment for HAE, *n* (%)[b]	5 (83)	6 (86)	4 (67)	15 (79)
Any C1-INH	1 (17)	1 (14)	1 (17)	3 (16)
Any androgen	0	2 (29)	1 (17)	3 (16)
Tranexamic acid	5 (83)	3 (43)	3 (50)	11 (58)
Mean age at diagnosis, y (SD)	34 (19)	29 (8)	30 (17)	31 (14)
Missed work or education in the past year due to HAE, *n* (%)	5 (83)	5 (71)	4 (67)	14 (74)

Abbreviations: BMI, body mass index; C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; SD, standard deviation.

[a]Baseline expert-confirmed angioedema attack rate was defined as (total number of expert-confirmed angioedema attacks experienced in the period between screening and first date/time of study drug dosing) × 28/(date of first dose - date of screening + 1).

[b]Long-term prophylactic therapies for the prevention of HAE attacks are not approved in Japan (except for tranexamic acid). Use of these medications for prophylaxis was likely off label.

TABLE 2 Summary of primary and secondary endpoints in the intent-to-treat population

Endpoint	Berotralstat 110 mg (*N* = 6)	Berotralstat 150 mg (*N* = 7)	Placebo (*N* = 6)
Primary endpoint			
Expert-confirmed attack rate (entire dosing period through 24 weeks)[a]			
Estimated rate	1.64	1.11	2.18
Percent rate reduction difference from placebo (95% CI)	24.6 (−14.0 to 50.1)	49.1 (20.4 to 67.5)	
Unadjusted *p* value	.181	.003	
Adjusted alpha level	.050	.025	
Statistically significant[b]	No	Yes	
Secondary endpoints			
Proportion of days with angioedema symptoms through 24 weeks[c]			
LS mean (standard error)	0.26 (0.05)	0.12 (0.05)	0.24 (0.05)
LS mean difference from placebo (95% CI)	0.02 (−0.14 to 0.18)	−0.12 (−0.28 to 0.04)	
Unadjusted *p* value	.814	.120	
Adjusted alpha level	NA[d]	.025	
Statistically significant[b]	NA[d]	No	
Expert-confirmed attack rate (effective dosing period through 24 weeks)[e]			
Estimated rate	1.66	1.16	2.20
Percent rate reduction difference from placebo (95% CI)	24.5 (−14.7 to 50.3)	47.6 (17.7 to 66.6)	
Unadjusted *p* value	.188	.005	
Adjusted alpha level	NA[d]	NA[d]	
Statistically significant[b]	NA[d]	NA[d]	
AE-QoL total score (change from baseline to week 24)[f]			
LS mean (standard error)	−9.47 (6.93)	−15.82 (6.42)	3.18 (6.83)
LS mean difference from placebo (95% CI)	−12.7 (−33.3 to 8.0)	−19.0 (−39.0 to −1.0)	
Unadjusted *p* value	.213	.061	
Adjusted alpha level	NA[d]	NA[d]	
Statistically significant[b]	NA[d]	NA[d]	

Abbreviations: AE-QoL, angioedema quality of life; ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSM, least-squares mean; NA, not applicable.

[a]Expert-confirmed angioedema attack rate was defined as (total number of expert-confirmed angioedema attacks experienced in the period between first date/time of study drug in part 1 and the first dose date/time in part 2 [or the last dose date/time of dose in part 1 + 24 h for patients who discontinued drug in part 1]) × 28/(date of first dose in part 2 [or date of last dose in part 1] - date of first dose in part 1 + 1). Statistical analysis was based on a negative binomial regression model. The number of expert-confirmed angioedema attacks was included as the dependent variable, the treatment was included as a fixed effect, baseline expert-confirmed attack rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

[b]A comparison is considered statistically significant if the unadjusted *p* value is less than the corresponding Hochberg-adjusted alpha level.

[c]For the proportion of days with angioedema symptoms, the difference was the LSM difference from an ANCOVA model with baseline expert-confirmed attack rate as a covariate and treatment included as a fixed effect.

[d]NA is due to the use of the Hochberg step-up procedure. Testing was stopped at the primary endpoint for the 110 mg dose because $p > .05$. Testing was stopped at the first secondary endpoint for the 150 mg dose (proportion of days with angioedema symptoms through 24 weeks) because $p > .025$.

[e]Expert-confirmed angioedema attack rate during the effective treatment period was defined as (total number of expert-confirmed angioedema attacks experienced in the period between study day 8 in part 1 and the first dose date/time in part 2 [or the last dose date/time in part 1 + 24 h for patients who discontinued drug in part 1]) × 28/(date of first dose in part 2 [or last dose date in part 1] − date of study day 8 in part 1 + 1). Statistical analysis was based on a negative binomial regression model. The number of expert-confirmed angioedema attacks was included as the dependent variable, the treatment was included as a fixed effect, baseline expert-confirmed attack rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

[f]For the change from baseline in AE-QoL total score at week 24, the difference was the LSM difference from a mixed-model repeated-measures analysis with expert-confirmed baseline attack rate, baseline AE-QoL, treatment group, visit and visit × treatment group interaction included as fixed effects, and patient included as a random effect.

Baseline demographics and disease characteristics were generally similar across treatment groups (Table 1). Patients were predominantly female (84%) and the mean baseline expert-confirmed HAE attack rate was 2.3 attacks/month across treatment groups. Overall, 79% of patients reported prior use of any prophylactic treatment for HAE, most commonly tranexamic acid (58%), androgens (16%), and plasma-derived C1-INH (16%).

3.2 | Efficacy

The model-estimated rates of expert-confirmed angioedema attack through 24 weeks were 1.64 attacks/month for the 110 mg dose group, 1.11 attacks/month for the 150 mg dose group, and 2.18 attacks/month for the placebo group. The primary endpoint was met for the 150 mg group, with reduction of expert-confirmed HAE attack rate by 49% compared with placebo (p = .003; Table 2). The 110 mg dose reduced the expert-confirmed HAE attack rate by 25% compared with placebo (p = .181). Reductions in expert-confirmed HAE attack rates from baseline with berotralstat 150 mg treatment were observed in month 1 and remained consistently lower relative to placebo throughout the entire 24-week dosing period (Figure 2).

As the primary endpoint did not meet statistical significance for the 110 mg dose, inferential statistical testing was not performed on the secondary efficacy endpoints for this dose. The result for the first secondary endpoint, proportion of days with angioedema

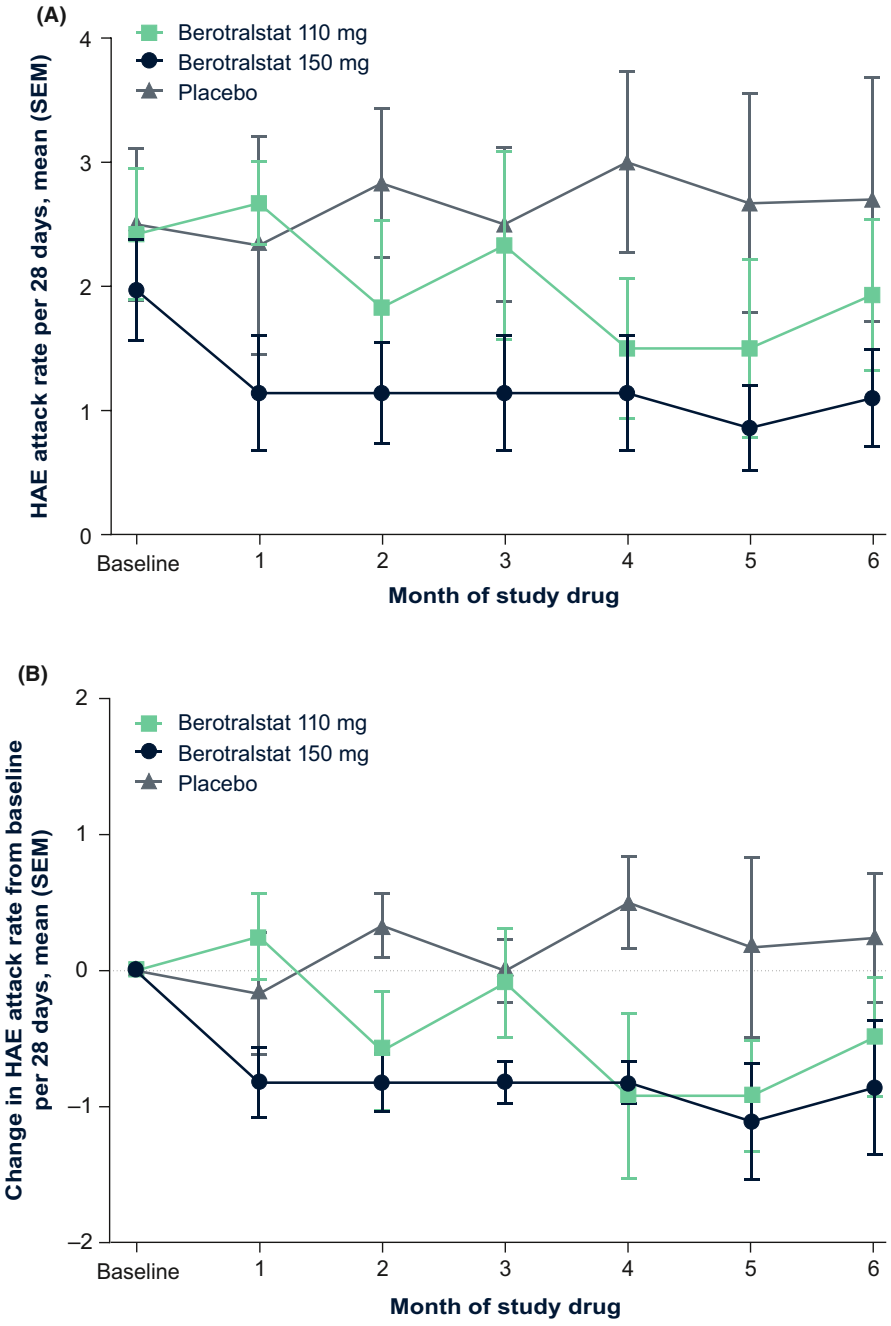


FIGURE 2 (A) Mean expert-confirmed attack rate; (B) change from baseline in expert-confirmed attack rate by month at week 24. Abbreviations: HAE, hereditary angioedema; SEM, standard error of the mean

symptoms, was not statistically significant for the 150 mg dose; therefore, statistical testing on the remaining secondary endpoints was stopped; reported *p* values for descending secondary endpoints are nominal. Reductions in expert-confirmed HAE attack rates over the effective treatment period (steady state, day 8 to week 24) relative to placebo were 25% (nominal $p = .188$) and 48% (nominal $p = .005$) for the 110 mg and 150 mg groups, respectively. These reductions were similar to those observed over the entire treatment period. In exploratory responder analyses, 57% of patients in the 150 mg group ($p = .070$) and 33% in the 110 mg group ($p = .455$) experienced a ≥50% reduction in adjusted HAE attack rate relative to baseline compared with 0% of patients in the placebo group. Reductions of ≥70% were observed in 29% of patients in the 150 mg dose group compared with 0% of patients in the 110 mg and placebo groups ($p = .462$ for 150 mg group vs. placebo). No patients in any treatment group achieved a ≥90% reduction.

The difference from placebo in the proportion of days with angioedema symptoms at week 24 was 0.02 days (nominal $p = .814$), equating to approximately 3 fewer symptom-free days over the 24-week dosing period for the 110 mg group; and −0.12 days ($p = .120$), equating to approximately 20 more symptom-free days over the 24-week dosing period for the 150 mg group. Both berotralstat treatment groups had average improvement in AE-QoL scores that exceeded the minimal clinically important difference (MCID; ≥6 points).[28] At week 24, 50% and 43% of patients had achieved the MCID in the 110 mg and 150 mg groups, respectively, compared with 17% of patients in the placebo group. The least-squares mean difference from placebo in AE-QoL scores was −12.7 (nominal $p = .213$) and −19.0 (nominal $p = .061$) for the 110 mg and 150 mg groups, respectively. Individual domain scores of the AE-QoL were improved for berotralstat-treated patients but were not statistically different from placebo, with the exception of 1 domain (fears/shame), where patients in the 150 mg group experienced a nominally significant improvement (Figure 3).

Patients in both the 110 mg and 150 mg groups had fewer angioedema attacks that required treatment with on-demand medication vs. placebo. The 110 mg and 150 mg doses reduced the rate of attacks requiring on-demand treatment (110 mg: 1.40 attacks/month, $p = .237$; 150 mg: 0.80 attacks/month, $p = .002$) vs. placebo (1.86 attacks/month; Table S1).

3.3 | Safety

All patients experienced TEAEs through 24 weeks of dosing (Table 3). The most frequently reported TEAEs in berotralstat-treated patients ($n = 13$) were nasopharyngitis ($n = 4$, 31%), cough ($n = 2$, 15%), abdominal pain ($n = 2$, 15%), diarrhea ($n = 2$, 15%), and pyrexia ($n = 2$, 15%). Drug-related TEAEs were reported in 2 patients in the 110 mg group (33%) and 2 patients in the 150 mg group (29%). No grade 4 TEAEs were reported in the study, and no grade 3 TEAEs were reported in either of the berotralstat treatment groups. One patient in the placebo group experienced a grade 3 decreased platelet count. One patient in the placebo group discontinued study drug before week 24 because of a grade 2 TEAE of urticaria that was considered possibly related to study drug.

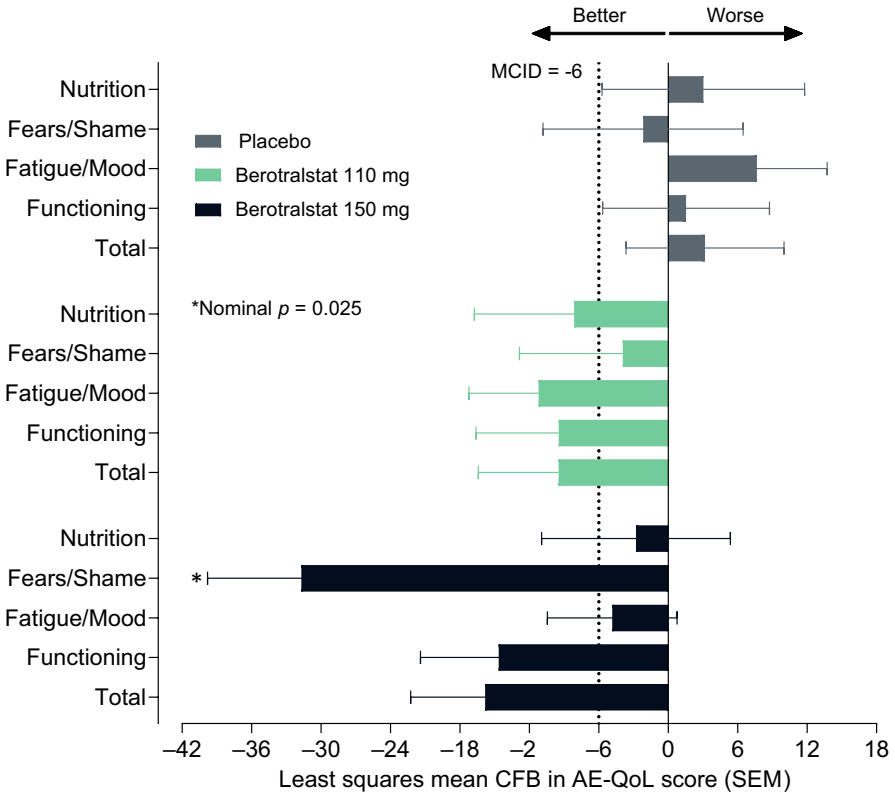


FIGURE 3 Angioedema quality of life scores, week 24 compared with baseline. Abbreviations: AE-QoL, angioedema quality of life; CFB, change from baseline; MCID, minimal clinically important difference; QoL, quality of life; SEM, standard error of the mean. The AE-QoL scores range from 0 to 100, and a decrease (change with a negative value) in AE-QoL questionnaire scores indicates an improvement in the patient's QoL. The MCID for the AE-QoL total score is 6 points.

With berotralstat treatment, the system organ class with the most TEAEs reported was GI disorders, inclusive of GI abdominal TEAEs. Overall, 3 patients treated with berotralstat 110 mg (50%) and 3 treated with berotralstat 150 mg (43%) experienced GI abdominal TEAEs, compared with 1 patient (17%) receiving placebo. GI abdominal TEAEs were predominantly mild in severity.

4 | DISCUSSION

This study demonstrated a favorable benefit-risk balance for oral once-daily berotralstat 150 mg as prophylactic HAE therapy. The berotralstat 150 mg dose significantly reduced HAE attacks (1.11 attacks/month) compared with placebo (2.18 attacks/month, $p = .003$). Reductions in expert-confirmed angioedema attack rates with the 150 mg dose were observed during the first month of treatment, were sustained through 24 weeks of dosing, and included a significant reduction in the rate of on-demand medication use (51%; $p = .006$). Additionally, more than half (57%) of patients treated with berotralstat 150 mg experienced a ≥50% relative reduction in HAE attack rates compared with 0 patients receiving placebo. Patients receiving berotralstat also reported improvements in QoL as assessed using an angioedema-specific questionnaire; however, with the exception of the fears/shame domain in the berotralstat 150 mg treatment group, these improvements were not statistically differentiated from placebo. Berotralstat was safe and generally well tolerated over 24 weeks.

The efficacy and safety data from the APeX-J trial are consistent with the results of the global phase 3 APeX-2 study.[25] Throughout 24 weeks in both trials, a clear dose response was observed with the 150 mg berotralstat dose over the 110 mg dose. In APeX-J, the 110 mg and 150 mg berotralstat doses reduced the rate of expert-confirmed HAE attacks by 25% ($p = .181$) and 49% ($p = .003$), respectively, compared with placebo. In APeX-2, the 110 mg and 150 mg berotralstat doses reduced confirmed HAE attacks by 30% ($p = .024$) and 44% ($p < .001$), respectively, compared with placebo.[25] In both APeX-2 and APeX-J trials, treatment with berotralstat was also shown to reduce the rates of attacks requiring on-demand treatment. Reduction in the number of attacks requiring on-demand treatment is particularly beneficial for Japanese patients due to limited access to approved on-demand therapies and the absence of approved, targeted, long-term prophylactic therapies in Japan.

The safety profile of berotralstat observed in APeX-J was consistent with what has been reported in the larger APeX-2 trial, and no new safety signals were observed in Japanese patients.[30]

The major limitation of this study was the small sample size due to the rare disease status of HAE in Japan. Several factors had an influence on patient enrollment, including limited awareness of HAE among physicians and a relatively small number of diagnosed HAE patients in Japan. Additionally, the treatment period (24 weeks) was relatively short for assessment of long-term prophylactic therapy. As the trial is still ongoing, longer-term data can be assessed once patients have completed 52 weeks of dosing. Nevertheless, a robust primary analysis outcome was observed for the 150 mg dose.

Overall, this study supports the use of oral berotralstat 150 mg once daily as an effective prophylactic treatment for the prevention

TABLE 3 Summary of TEAEs in the safety population

Events, *n* (%)	Berotralstat 110 mg (*N* = 6)	Berotralstat 150 mg (*N* = 7)	Placebo (*N* = 6)
TEAE	6 (100)	7 (100)	6 (100)
Drug-related TEAE[a]	2 (33)	2 (29)	2 (33)
Grade 3 or 4 TEAE[b]	0	0	1 (17)
Drug-related grade 3 or 4 TEAE	0	0	0
TESAE[c]	1 (17)	0	0
Drug-related TESAE	0	0	0
TEAE leading to discontinuation of study drug	0	0	1 (17)
Any GI abdominal TEAE[d]	3 (50)	3 (43)	1 (17)
Most frequent TEAEs, *n* (%)			
Nasopharyngitis	2 (33)	2 (29)	4 (67)
Abdominal discomfort	1 (17)	0	1 (17)
Abdominal pain	1 (17)	1 (14)	0
Cough	2 (33)	0	0
Diarrhea	1 (17)	1 (14)	0
Headache	1 (17)	0	1 (17)
Pyrexia	1 (17)	1 (14)	0
Urticaria	0	1 (14)	1 (17)

Abbreviations: AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

[a]A drug-related TEAE was defined as any AE where the investigator defined the relationship to blinded study drug as possibly related, probably related, or definitely related. Berotralstat 110 mg: abdominal discomfort, diarrhea, nausea, headache; berotralstat 150 mg: abdominal pain upper, gastritis, pyrexia, somnolence; placebo: abdominal discomfort, urticaria.

[b]AE severity was assessed using the United States National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases Adult Toxicity Tables (Draft, November 2007).

[c]TESAE events were defined per standard regulatory definition (ie, any adverse event/reaction that results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event in the medical judgment of the investigator). Any graded abnormality that occurs following the initiation of study drug and represents at least one-grade increase from the baseline assessment is defined as treatment emergent.

[d]GI abdominal AEs were any AEs with a preferred term within the MedDRA 19.1 hierarchy under the High-level Group Terms of 1) GI signs and symptoms or 2) GI motility and defecation conditions.

of angioedema attacks in patients with HAE in Japan. Because of the current lack of targeted, long-term prophylactic therapies in Japan, these results suggest that berotralstat would be an important advance in the management of HAE in Japan, serving a significant unmet need in this community.

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CONFLICT OF INTEREST

DH reports speaker fees from CSL Behring, Kyowa Kirin, Otsuka, Shire, and Takeda outside the submitted work. GC, MC, SCM, SMD, EN, SVD, LR, JB, HI, PC, and WPS are employees of BioCryst Pharmaceuticals. GC, EN, LR, and WPS hold stock options in BioCryst Pharmaceuticals. MH reports personal fees from BioCryst Pharmaceuticals during the conduct of the study; personal fees from Shire/Takeda; and grants and personal fees from CSL Behring, outside the submitted work; and a grant of the Ministry of Health, Labour and Welfare of Japan. IO, YSuzuki, TF, KK, EM, SM, OI, YSasaki, and MT have nothing to disclose.

AUTHOR CONTRIBUTION

IO, MH, MC, SCM, SMD, SVD, PC, and WPS participated in the conception and design of the study. GC, MC, SCM, SMD, EN, SVD, LR, JB, HI, PC, and WPS oversaw the conduct of the study and/or were involved in the analysis, interpretation, and reporting of data. SCM oversaw the statistical analysis. IO, DH, YSuzuki, TF, KK, EM, SM, OI, YSasaki, and MT were study investigators who were responsible for the recruitment and follow-up of patients and acquisition of data; MH adjudicated all HAE events. GC wrote the first draft of the manuscript; all authors reviewed and approved the manuscript.

DATA AVAILABILITY STATEMENT

Data transparency information is available at http://www.biocryst.com/.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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