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

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21 **Abstract**

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

26 **Methods:** APeX-J is a phase 3 randomized, double-blind, placebo-controlled, parallel-group, three-
27 part trial conducted in Japan (University Hospital Medical Information Network identifier,
28 UMIN000034869; ClinicalTrials.gov identifier, NCT03873116). Patients with a clinical diagnosis of
29 type 1 or 2 HAE underwent a prospective run-in period of 56 days to determine eligibility, allowing
30 enrollment of those with ≥ 2 expert-confirmed angioedema attacks. Patients were randomly assigned
31 (1:1:1) and stratified by baseline attack rate (≥ 2 vs < 2 expert-confirmed attacks/month between
32 screening and randomization) to receive once-daily berotralstat 110 mg, berotralstat 150 mg, or
33 placebo. The primary endpoint was the rate of expert-confirmed angioedema attacks during dosing in
34 the 24-week treatment period.

35 **Results:** Nineteen patients were randomized to receive once-daily berotralstat 110 mg (n=6),
36 berotralstat 150 mg (n=7), or placebo (n=6). Treatment with berotralstat 150 mg significantly reduced
37 HAE attacks relative to placebo (1.11 vs 2.18 attacks/month, $P=0.003$). The most frequently reported
38 treatment-emergent adverse events (TEAEs) in berotralstat-treated patients (n=13) were
39 nasopharyngitis (n=4, 31%), abdominal pain, cough, diarrhea, and pyrexia (n=2 each, 15%).

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

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46 Introduction

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

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

63 In Japan, HAE is estimated to affect 2500 patients, and the recognition of HAE by physicians
64 is low.¹⁵⁻¹⁷ Further, only 2 on-demand therapies are currently approved by the Japanese Ministry of
65 Health, Labour and Welfare (MHLW) for the treatment of acute HAE attacks—IV plasma-derived C1-
66 INH and SC icatibant—and only icatibant is approved for self-administration.^{18,19} If the angioedema
67 attack worsens after self-administration of icatibant, patients must visit their healthcare providers to
68 receive plasma-derived C1-INH, and patients often live in fear that they will not arrive in time to the
69 hospital or clinic. Additionally, the number of hospitals where HAE patients can receive plasma-
70 derived C1-INH is unacceptably low and some prefectures have no medical facilities with disclosed
71 stock of plasma-derived C1-INH.^{15,16} Both the 2010 and updated 2014 guidelines for HAE by the
72 Japanese Association for Complement Research recommend danazol and tranexamic acid for
73 prophylaxis of attacks in patients with a history of laryngeal edema, however, danazol is not
74 approved by the MHLW, and tranexamic acid is indicated for symptoms of erythema, itching, and
75 swelling associated with diseases such as eczema, urticaria, drug eruption, and toxicoderma.²⁰⁻²³
76 Therefore, there is an urgent need for targeted prophylactic therapies to reduce the frequency and
77 severity of angioedema attacks for patients in Japan.

78 Berotralstat (BCX7353) is an oral, highly selective inhibitor of plasma kallikrein in
79 development for prophylaxis of angioedema attacks in patients with HAE, with pharmacological
80 characteristics that support once-daily dosing.²⁴ The phase 3 APeX-2 trial was designed to assess
81 the efficacy and safety of 2 once-daily doses of berotralstat (110 mg and 150 mg) for prophylaxis of
82 angioedema attacks in patients with HAE in North America and Europe. At the primary analysis (24
83 weeks of dosing), both doses of berotralstat significantly reduced the frequency of HAE attacks
84 compared with placebo (1.65 attacks/month at 110 mg [$P=0.024$] and 1.31 attacks/month at 150 mg
85 [$P<0.001$] vs 2.35 attacks/month with placebo) and were found to be safe and generally well
86 tolerated.²⁵

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

91

METHODS

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).

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

124 initiation during study. Prophylaxis was defined as administration of medication in the absence of
125 symptoms of an angioedema attack. Acute use of a C1-INH therapy for the treatment of angioedema
126 attacks was not excluded at any time, nor was the use of C1-INH for preprocedural prophylaxis for
127 an unplanned procedure.

128 **Procedures**

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

137 Details of angioedema attacks, including time of event, symptoms, anatomical location,
138 severity, and treatments were recorded by the patient in an electronic diary. Within approximately 2
139 business days of the end of each attack, patients were contacted by the investigator to discuss the
140 attack. An independent expert (an experienced HAE treater in Japan) was selected by the sponsor to
141 review all reported angioedema attacks. The electronic diary and any investigator-collected
142 information were used by the independent expert to either confirm or reject the attack. Angioedema
143 attacks were treated in accordance with the medical management plan advised by the investigator or
144 treating physician.

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

147 **Outcomes**

148 The primary efficacy endpoint was the rate of expert-confirmed angioedema attacks during
149 the 24-week dosing period. Secondary endpoints included the number and proportion of days with
150 angioedema symptoms, the rate of expert-confirmed angioedema attacks during dosing in the
151 effective treatment period (steady state, beginning on day 8), and the change from baseline in quality
152 of life at week 24 as assessed by the Angioedema Quality of Life (AE-QoL) questionnaire.^{27,28}
153 Exploratory endpoints included the use of on-demand medications to treat angioedema attacks and
154 the proportion of $\geq 50\%$ responders to study drug. The proportion of $\geq 70\%$ and $\geq 90\%$ responders
155 were added as exploratory endpoints in a protocol amendment.

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

164 **Statistical analysis**

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

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

182 The baseline requirements for expert-confirmed attack rate had 2 additional requirements not
183 applied to the entire dosing period on-study attacks: (1) attacks had to be unique, and (2) require
184 treatment, medical attention, or cause functional impairment. To allow for a more direct comparison
185 of angioedema attack rates occurring during the baseline and dosing periods, the 2 additional
186 requirements for expert-confirmed baseline attacks were applied programmatically to the on-study
187 expert-confirmed attacks occurring during the dosing period, resulting in an adjusted expert-
188 confirmed attack rate. Adjusted expert-confirmed attack rates were used to compare on-study attack
189 rates to baseline attack rates for the exploratory $\geq 50\%$, $\geq 70\%$, and $\geq 90\%$ responder endpoints.

190 Primary and secondary endpoints were tested hierarchically, with the type 1 error rate
191 controlled at the study level using a combination of hierarchical testing and the Hochberg
192 procedure.³¹ For the primary endpoint, the 2 berotralstat doses were tested at the $\alpha = 0.05$ level,
193 comparing active treatment to placebo. If the maximum of the 2 P values was ≤ 0.05 , the null
194 hypothesis of no difference between the attack rate for patients on active and placebo treatment was
195 rejected for both doses, and testing proceeded to the next endpoint in the hierarchy with $\alpha = 0.05$. If

the maximum of the 2 P values was >0.05 but the minimum of the 2 P values was <0.025 , the null hypothesis for the dose with $P<0.025$ was rejected, and testing for only that dose proceeded to the next endpoint in the hierarchy with $\alpha = 0.025$. 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.

206

207

RESULTS

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.

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%).

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 ($P=0.003$; **Table 2**). The 110-mg dose reduced the expert-confirmed HAE attack rate by 25% compared with placebo ($P=0.181$). 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**).

228 As the primary endpoint did not meet statistical significance for the 110-mg dose, inferential
229 statistical testing was not performed on the secondary efficacy endpoints for this dose. The result for
230 the first secondary endpoint, proportion of days with angioedema symptoms, was not statistically
231 significant for the 150-mg dose, therefore, statistical testing on the remaining secondary endpoints
232 was stopped; reported *P* values for descending secondary endpoints are nominal. Reductions in
233 expert-confirmed HAE attack rates over the effective treatment period (steady state, day 8 to week
234 24) relative to placebo were 25% (nominal *P*=0.188) and 48% (nominal *P*=0.005) for the 110-mg and
235 150-mg groups, respectively. These reductions were similar to those observed over the entire
236 treatment period. In exploratory responder analyses, 57% of patients in the 150-mg group (*P*=0.070)
237 and 33% in the 110-mg group (*P*=0.455) experienced a ≥50% reduction in adjusted HAE attack rate
238 relative to baseline compared with 0% of patients in the placebo group. Reductions of ≥70% were
239 observed in 29% of patients in the 150-mg dose group compared with 0% of patients in the 110-mg
240 and placebo groups (*P*=0.462 for 150-mg group vs placebo). No patients in any treatment group
241 achieved a ≥90% reduction.

242 The difference from placebo in the proportion of days with angioedema symptoms at week 24
243 was 0.02 days (nominal *P*=0.814), equating to approximately 3 fewer symptom-free days over the
244 24-week dosing period for the 110-mg group; and -0.12 days (*P*=0.120), equating to approximately
245 20 more symptom-free days over the 24-week dosing period for the 150-mg group. Both berotralstat
246 treatment groups had average improvement in AE-QoL scores that exceeded the minimal clinically
247 important difference (MCID; ≥6 points).²⁸ At week 24, 50% and 43% of patients had achieved the
248 MCID in the 110-mg and 150-mg groups, respectively, compared with 17% of patients in the placebo
249 group. The least squares mean difference from placebo in AE-QoL scores was -12.7 (nominal
250 *P*=0.213) and -19.0 (nominal *P*=0.061) for the 110-mg and 150-mg groups, respectively. Individual
251 domain scores of the AE-QoL were improved for berotralstat-treated patients but were not
252 statistically different from placebo, with the exception of 1 domain (fears/shame), where patients in
253 the 150-mg group experienced a nominally significant improvement (**Figure 3**).

254 Patients in both the 110-mg and 150-mg groups had fewer angioedema attacks that required
255 treatment with on-demand medication versus placebo. The 110-mg and 150-mg doses reduced the
256 rate of attacks requiring on-demand treatment (110 mg: 1.40 attacks/month, *P*=0.237; 150 mg: 0.80
257 attacks/month, *P*=0.002) versus placebo (1.86 attacks/month; Supplemental Table 1).

258

259 **Safety**

260 All patients experienced TEAEs through 24 weeks of dosing (**Table 3**). The most frequently
261 reported TEAEs in berotralstat-treated patients (n=13) were nasopharyngitis (n=4, 31%), cough (n=2,
262 15%), abdominal pain (n=2, 15%), diarrhea (n=2, 15%), and pyrexia (n=2, 15%). Drug-related TEAEs
263 were reported in 2 patients in the 110-mg group (33%) and 2 patients in the 150-mg group (29%). No
264 grade 4 TEAEs were reported in the study, and no grade 3 TEAEs were reported in either of the
265 berotralstat treatment groups. One patient in the placebo group experienced a grade 3 decreased
266 platelet count. One patient in the placebo group discontinued study drug before week 24 because of
267 a grade 2 TEAE of urticaria that was considered possibly related to study drug.

268 With berotralstat treatment, the system organ class with the most TEAEs reported was GI
269 disorders, inclusive of GI abdominal TEAEs. Overall, 3 patients treated with berotralstat 110 mg
270 (50%) and 3 treated with berotralstat 150 mg (43%) experienced GI abdominal TEAEs, compared
271 with 1 patient (17%) receiving placebo. GI abdominal TEAEs were predominantly mild in severity.

272 273 **DISCUSSION**

274 This study demonstrated a favorable benefit-risk balance for oral once-daily berotralstat 150
275 mg as prophylactic HAE therapy. The berotralstat 150-mg dose significantly reduced HAE attacks
276 (1.11 attacks/month) compared with placebo (2.18 attacks/month, $P=0.003$). Reductions in expert-
277 confirmed angioedema attack rates with the 150-mg dose were observed during the first month of
278 treatment, were sustained through 24 weeks of dosing, and included a significant reduction in the
279 rate of on-demand medication use (51%; $P=0.006$). Additionally, more than half (57%) of patients
280 treated with berotralstat 150 mg experienced a $\geq 50\%$ relative reduction in HAE attack rates
281 compared with 0 patients receiving placebo. Patients receiving berotralstat also reported
282 improvements in QoL as assessed using an angioedema-specific questionnaire; however, with the
283 exception of the fears/shame domain in the berotralstat 150-mg treatment group, these
284 improvements were not statistically differentiated from placebo. Berotralstat was safe and generally
285 well tolerated over 24 weeks.

286 The efficacy and safety data from the APeX-J trial are consistent with the results of the global
287 phase 3 APeX-2 study.²⁵ Throughout 24 weeks in both trials, a clear dose response was observed
288 with the 150-mg berotralstat dose over the 110-mg dose. In APeX-J, the 110-mg and 150-mg
289 berotralstat doses reduced the rate of expert-confirmed HAE attacks by 25% ($P=0.181$) and 49%
290 ($P=0.003$), respectively, compared with placebo. In APeX-2, the 110-mg and 150-mg berotralstat
291 doses reduced confirmed HAE attacks by 30% ($P=0.024$) and 44% ($P<0.001$), respectively,

292 compared with placebo.²⁵ In both APeX-2 and APeX-J trials, treatment with berotralstat was also
293 shown to reduce the rates of attacks requiring on-demand treatment. Reduction in the number of
294 attacks requiring on-demand treatment is particularly beneficial for Japanese patients due to limited
295 access to approved on-demand therapies and the absence of approved, targeted, long-term
296 prophylactic therapies in Japan.

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

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

306 Overall, this study supports the use of oral berotralstat 150 mg once daily as an effective
307 prophylactic treatment for the prevention of angioedema attacks in patients with HAE in Japan.
308 Because of the current lack of targeted, long-term prophylactic therapies in Japan, these results
309 suggest that berotralstat would be an important advance in the management of HAE in Japan,
310 serving a significant unmet need in this community.

311

312 **Contributors**

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

320

321 **Conflict of Interest Statement**

322 DH reports speaker fees from CSL Behring, Kyowa Kirin, Otsuka, Shire, and Takeda outside
323 the submitted work. GC, MC, SCM, SMD, EN, SVD, LR, JB, HI, PC, and WPS are employees of

324 BioCryst Pharmaceuticals. GC, EN, LR, and WPS hold stock options in BioCryst Pharmaceuticals.
325 MH reports personal fees from BioCryst Pharmaceuticals during the conduct of the study; personal
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329 330 **Data Sharing**

331 The study protocol will be available at [https://link.edgepilot.com/s/587ec4f7/-MHLLLe1ickyHqoM5q-](https://link.edgepilot.com/s/587ec4f7/-MHLLLe1ickyHqoM5q-URBQ?u=https://www.biocryst.com/our-focus/scientific-publications/)
332 [URBQ?u=https://www.biocryst.com/our-focus/scientific-publications/](https://www.biocryst.com/our-focus/scientific-publications/)
333 beginning one month and ending 12 months following publication. Individual patient data will not be
334 available.

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414 **Table 1.** Baseline characteristics of the intent-to-treat population

Characteristic	Berotralstat			
	110 mg (N=6)	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) [†]	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 (%) [‡]	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)

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

[†]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). [‡]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)	150 mg (N=7)	Placebo (N=6)
Primary endpoint			
Expert-confirmed attack rate (entire dosing period through 24 weeks) [†]			
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 <i>P</i> value	0.181	0.003	
Adjusted alpha level	0.050	0.025	
Statistically significant [‡]	No	Yes	
Secondary endpoints			
Proportion of days with angioedema symptoms through 24 weeks [§]			
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 <i>P</i> value	0.814	0.120	
Adjusted alpha level	NA ^{††}	0.025	

Statistically significant [‡]	NA ^{††}	No	
Expert-confirmed attack rate (effective dosing period through 24 weeks) ^{††}			
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 <i>P</i> value	0.188	0.005	
Adjusted alpha level	NA ^{††}	NA ^{††}	
Statistically significant [‡]	NA ^{††}	NA ^{††}	
AE-QoL total score (change from baseline to week 24) ^{††}			
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 <i>P</i> value	0.213	0.061	
Adjusted alpha level	NA ^{††}	NA ^{††}	
Statistically significant [‡]	NA ^{††}	NA ^{††}	

AE-QoL, Angioedema Quality of Life; ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSM, least squares mean; NA, not applicable.

[†]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 hours 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. [‡]A comparison is considered statistically significant if the unadjusted *P* value is less than the corresponding Hochberg-adjusted alpha level. [§]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. ^{††}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 hours 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. ^{††}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 $P>0.05$. Testing was stopped at the first secondary endpoint for the 150-mg dose (proportion of days with angioedema symptoms through 24 weeks) because $P>0.025$. ^{‡‡}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 $\times$ treatment group interaction included as fixed effects, and patient included as a random effect.

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Table 3. Summary of TEAEs in the safety population

	Berotralstat		
	110 mg	150 mg	Placebo
Events, n (%)	(N=6)	(N=7)	(N=6)
TEAE	6 (100)	7 (100)	6 (100)
Drug-related TEAE [†]	2 (33)	2 (29)	2 (33)

437	Grade 3 or 4 TEAE [‡]	0	0	1 (17)
	Drug-related grade 3 or 4 TEAE	0	0	0
	TESAE [§]	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 [¶]	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)

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

[‡]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. [‡]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). [§]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. [¶]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.

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FIGURES

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

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

Figure 3. AE-QoL scores, week 24 compared with baseline. 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.

all_14670_11.pdf
Patients screened
N=25

Screen failures, n=6
Inclusion/Exclusion criteria, n=5
Withdrawn consent, n=1

Patients randomized
N=19

**Berotrastat 110 mg
(N=6)**

**Berotrastat 150 mg
(N=7)**

**Placebo
(N=6)**

6 received at least 1 dose

7 received at least 1 dose

6 received at least 1 dose

0 discontinued dosing
in part 1

0 discontinued dosing
in part 1

1 discontinued dosing in part 1
TEAE of urticaria

6 completed dosing
in part 1

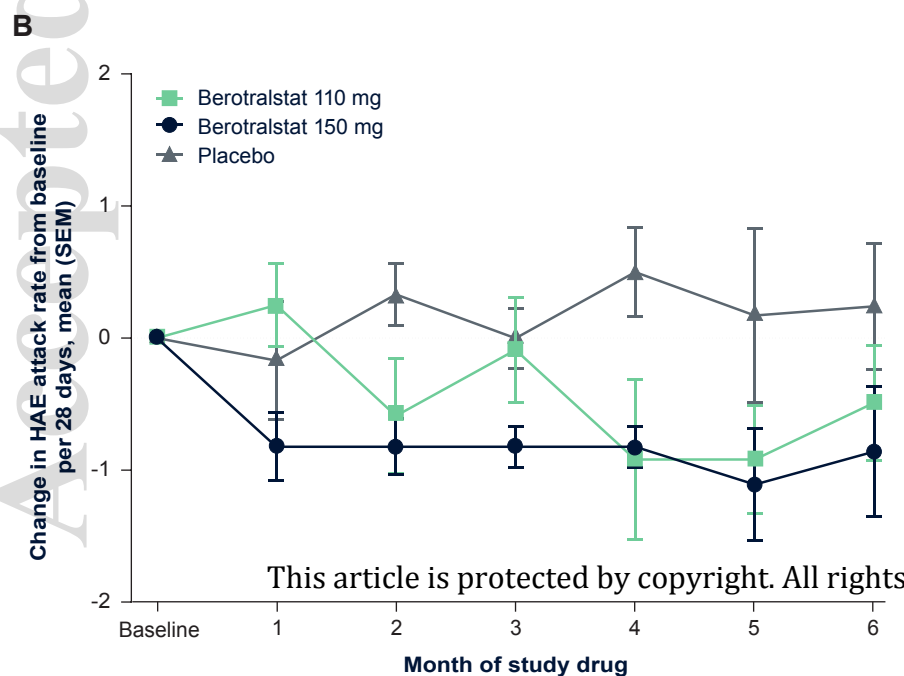
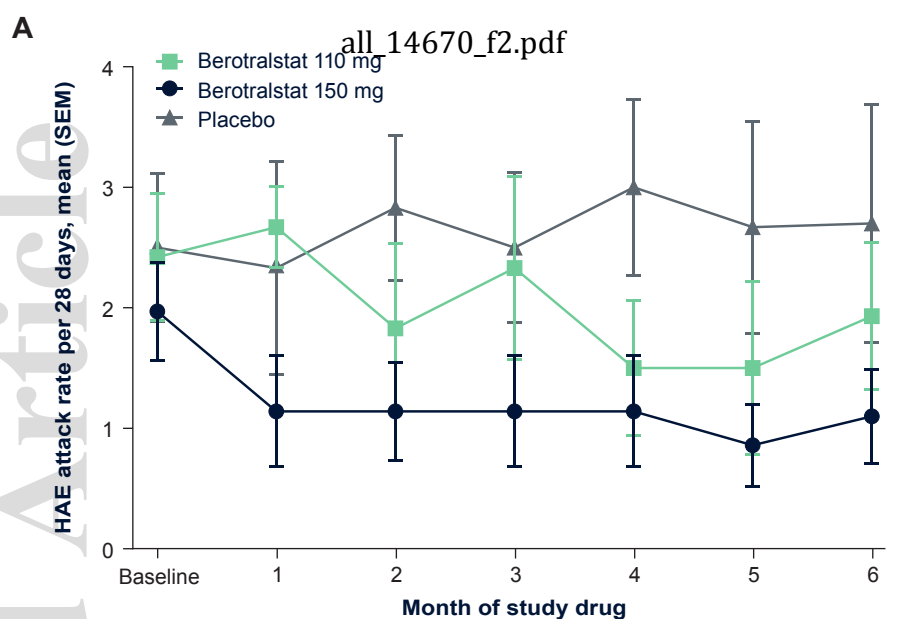
7 completed dosing
in part 1

5 completed dosing
in part 1

ITT population

Safety population

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Better ← → Worse

MCID = -6

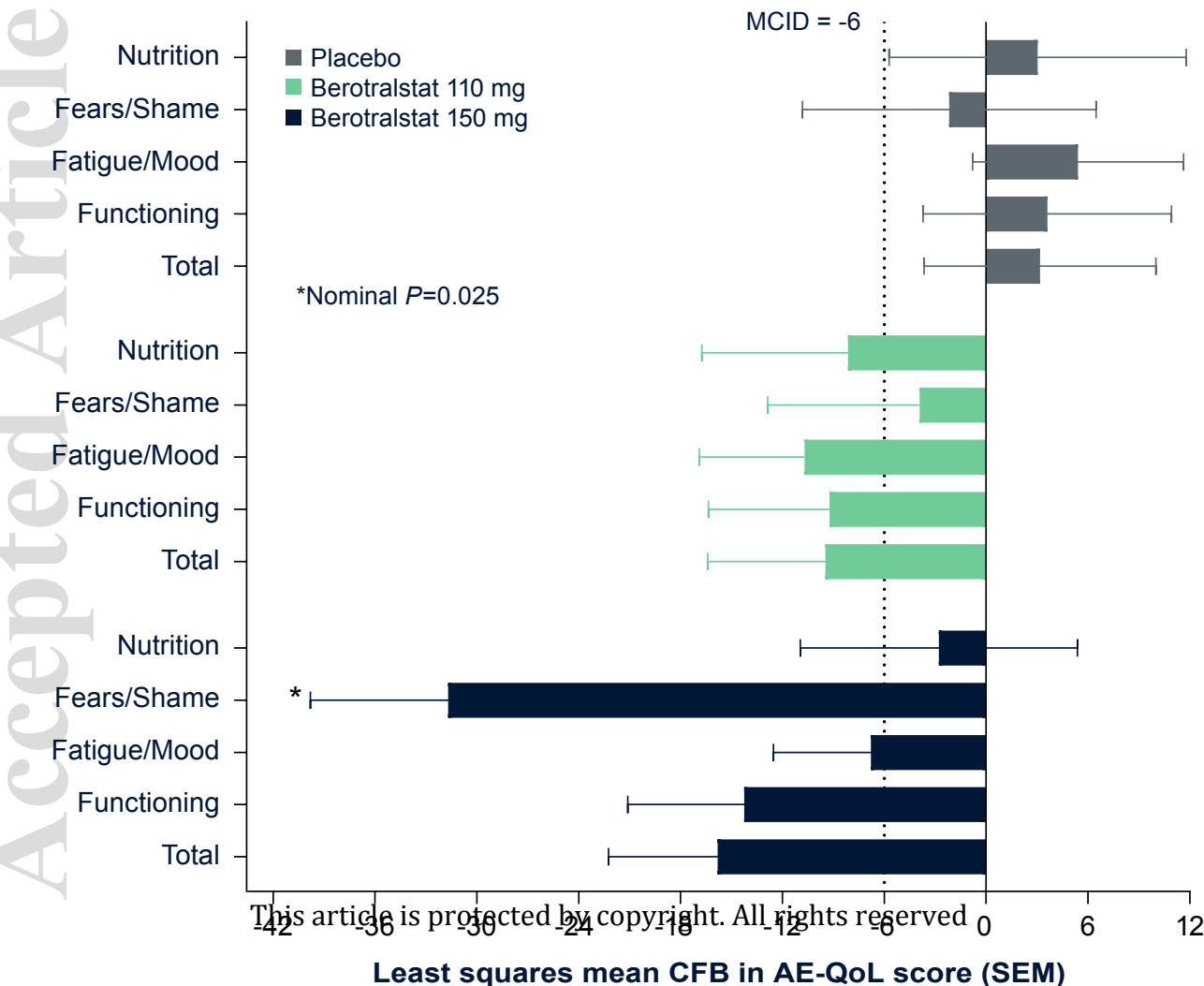
■ Placebo
■ Berotralstat 110 mg
■ Berotralstat 150 mg

*Nominal $P=0.025$

*

42 36 30 24 18 12 6 0 6 12

Least squares mean CFB in AE-QoL score (SEM)



SUPPORTING INFORMATION

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

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Supplemental Table 1. Summary of Rates of Expert-confirmed Angioedema Events That Required SOC-Rx and Rate of SOC-Rx Use, Entire Dosing Period (ITT Population)

SOC-Rx	Berotralstat						Placebo (N=6)
	110 mg (N=6)			150 mg (N=7)			
	Rate per 28 days [†]	Active vs placebo, % (95% CI)	P value	Rate per 28 days [†]	Active vs placebo, % (95% CI)	P value	
Expert-confirmed event rate ^{†,‡}	1.64	-24.6% (-50.1 to 14.0)	0.181	1.11	-49.1% (-67.5 to -20.4)	0.003	2.18
Rate of expert-confirmed events treated with SOC-Rx ^{†,‡}	1.40	-24.9% (-53.3 to 20.7)	0.237	0.80	-56.9% (-74.5 to -27.2)	0.002	1.86
SOC-Rx rate of use (doses/month) ^{†,‡}	1.86	-16.2% (-47.9 to 34.8)	0.466	1.09	-51.0% (-70.6 to -18.6)	0.006	2.22

CI, confidence interval; ITT, intent to treat; SOC-Rx, hereditary angioedema standard-of-care acute event medication.

[†]Statistical analysis was based on a negative binomial regression model. The number of expert-confirmed angioedema events, expert-confirmed events treated with SOC-Rx, or number of doses of SOC-Rx was included as the dependent variable, the treatment was included as a fixed effect, baseline expert-confirmed event rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

[‡]Estimated rate from negative binomial regression model.