Relative Reductions in Attack Rate With Prophylactic Berotralstat (BCX7353) in Patients With Hereditary Angioedema: Responder Analysis From the APeX-2 Study

William R. Lumry,[1] Marcus Maurer,[2] Bruce Zuraw,[3] Aleena Banerji,[4] Marc Riedl,[3] Douglas Johnston,[5] Emel Aygören-Pürsün,[6] Joshua Jacobs,[7] Richard G. Gower,[8] H. James Wedner,[9] Karl V. Sitz,[10] Marcus Magerl,[2] Melanie Cornpropst,[11] Jennifer A. Elder,[12] Heather Iocca,[11] Eniko Nagy,[11] Sharon Murray,[11] Phil Collis,[11] William P. Sheridan,[11] Sandra C. Christiansen,[3] on behalf of the APeX-2 Study Investigators

[1]Allergy & Asthma Specialists of Dallas, Dallas, TX, USA; [2]Charité Universitätsmedizin, Berlin, Germany; [3]UC San Diego Health, San Diego, CA, USA; [4]Massachusetts General Hospital, Boston, MA, USA; [5]Asthma & Allergy Specialists, Charlotte, NC, USA; [6]University Hospital Frankfurt, Goethe University, Frankfurt, Germany; [7]Allergy & Asthma Medical Group, Walnut Creek, CA, USA; [8]Marycliff Clinical Research, Spokane, WA, USA; [9]The Asthma and Allergy Center, Washington University, St Louis, MO, USA; [10]Little Rock Allergy & Asthma Center, Little Rock, AR, USA; [11]BioCryst Pharmaceuticals, Inc, Durham, NC, USA; [12]PharPoint Research, Inc, Wilmington, NC, USA

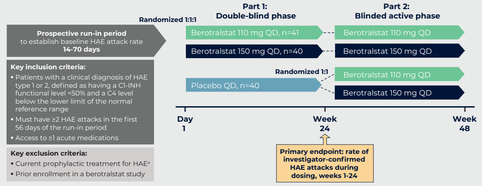
INTRODUCTION

- Hereditary angioedema (HAE) is a rare disease characterized by unpredictable, potentially life-threatening recurrent swelling attacks most commonly affecting the extremities, face, abdomen, and larynx.[1,2]
- Angioedema attacks are mediated by dysregulation of the bradykinin-forming pathway.[3]
- Uncontrolled plasma kallikrein activity leads to overproduction of bradykinin, which results in vasodilation, vascular leakage, and consequent swelling.[3,4]
- HAE is variable in both phenotype and in its response to treatment.[1,5]
- Berotralstat (BCX7353) is an oral, once-daily, highly selective inhibitor of plasma kallikrein in development for prophylaxis of HAE attacks.
- Berotralstat significantly reduced the frequency of HAE attacks compared with placebo and was found to be safe and generally well tolerated in the APeX-2 study.[6,7]
- The ad hoc analysis from the APeX-2 study presented here aims to assess the predictive value of baseline characteristics on the rates of investigator-confirmed attacks and responder status (≥50% or ≥70% reduction in attack rate relative to baseline) with berotralstat treatment.

METHODS

- APeX-2 is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study in patients with HAE (**Figure 1**).

Figure 1. APeX-2 Study Design



C1-INH, C1 esterase inhibitor; C4, complement 4; HAE, hereditary angioedema; QD, once daily. [a]Prophylactic treatments constituting exclusion included using C1-INH within 14 days before screening visit, using androgens or tranexamic acid within 28 days before screening visit, or initiating use of any of these drugs for prophylaxis during the trial.

- Baseline attack rate was prospectively established during a run-in period of up to 70 days before randomization. Prespecified criteria detailed characteristics of HAE attacks that must be present for an attack to be eligible for investigator confirmation during the run-in period.
- Eligible patients were randomized 1:1:1 to berotralstat 110 mg or 150 mg, or placebo once daily for 24 weeks (part 1). At week 24, patients were continued on the same dose of berotralstat or, for placebo patients, randomized 1:1 to either 110 mg or 150 mg of berotralstat.
- Baseline characteristics were assessed for their ability to predict efficacy outcomes. These included treatment group, age, prior androgen use (yes/no), prior prophylactic medicine within 30 days of screening (yes/no), baseline attack rate, categorized baseline attack rate (<2 or ≥2 attacks/month), geographic region (Europe vs North America), race (white or other), weight, weight group (≥ or < median weight of 78.96 kg), body mass index (BMI), BMI group (normal weight, overweight, obese), sex (male/female), C1 esterase inhibitor (C1-INH) functional level at screening, and complement 4 (C4) level at screening (< lower limit of normal [LLN] vs ≥ LLN).
- The primary efficacy endpoint evaluated was the rate of investigator-confirmed HAE attacks over 24 weeks.

METHODS (CONTINUED)

- For the effect of baseline characteristics on the primary analysis, negative binomial regression models were constructed with investigator-confirmed attack rate during part 1 as the outcome variable and the log of treatment duration as the offset variable, with independent baseline variables initially included one at a time in univariate models. A final multivariable model was obtained using a stepwise regression process with a 20% significance level for a variable to enter the model and a 15% significance level for a variable to stay in the model.
- The proportion of responders to study drug was an exploratory endpoint. A responder was defined as a patient who had a reduction of ≥50% (prespecified) or ≥70% (ad hoc) in the rate of adjusted investigator-confirmed HAE attacks compared with baseline (relative reduction).
- Adjusted investigator-confirmed attack rate was calculated by programmatically applying the 2 additional criteria used in calculation of the baseline attack rate (discrete attacks requiring treatment or causing functional impairment) to the postbaseline period.
- The effect of baseline characteristics on the responder status was evaluated using logistic regression, separately for responses of ≥50% and ≥70% relative reductions, initially including one independent variable at a time in univariate models. Final multivariable models for each response were obtained using stepwise logistic regression, considering the same independent variables as for the primary analysis and using the same significance levels for a variable to enter or stay in the model as were used for the primary endpoint model.

RESULTS

- 121 patients were randomized to treatment (**Table 1**).

Table 1. Summary of Baseline Demographics and Disease Characteristics

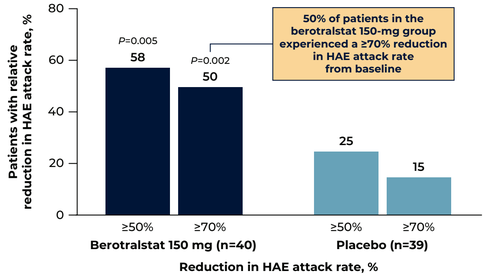
Patient characteristic, n (%)[a]	Berotralstat 110 mg (n=41)	Berotralstat 150 mg (n=40)	Placebo (n=40)	Total (N=121)
Age, mean (SD), y	40 (18)	40 (14)	45 (14)	42 (15)
Female	30 (73)	23 (58)	27 (68)	80 (66)
Race				
White	38 (93)	38 (95)	37 (93)	113 (93)
Region				
North America	32 (78)	27 (68)	28 (70)	87 (72)
Europe	9 (22)	13 (33)	12 (30)	34 (28)
Weight, mean (SD), kg	79 (22)	88 (20)	85 (21)	84 (21)
BMI, mean (SD), kg/m²	28 (7)	30 (7)	29 (7)	29 (7)
BMI 18.5 to 24.9 kg/m² (normal weight)	19 (46)	8 (20)	12 (30)	39 (32)
BMI 25 to 29.9 kg/m² (overweight)	8 (20)	16 (40)	14 (35)	38 (31)
BMI ≥30 kg/m² (obese)	14 (34)	16 (40)	13 (33)	43 (36)
Prior prophylactic treatment use within 30 days	10 (24)	12 (30)	11 (28)	33 (27)
Any prior androgen use	19 (46)	21 (53)	25 (63)	65 (54)
Baseline attack rate, mean (SD), attacks/month	2.97 (1.36)	3.06 (1.56)	2.91 (1.12)	2.98 (1.35)
≥2 HAE attacks/month	28 (68)	30 (75)	27 (68)	85 (70)

BMI, body mass index; C1-INH, C1 esterase inhibitor; C4, complement 4; HAE, hereditary angioedema; SD, standard deviation. [a]Unless otherwise indicated. C1-INH function and C4 levels were evaluated at screening for all patients and contributed to determination of eligibility.

RESULTS (CONTINUED)

- 120 patients received ≥1 dose of study drug.
- Both berotralstat groups met the primary efficacy endpoint with significantly lower rates of investigator-confirmed attacks over 24 weeks compared with the placebo group (110 mg, 1.65 attacks/month, P=0.024; 150 mg, 1.31 attacks/month, P<0.001; placebo, 2.35 attacks/month; negative binomial regression model). Subsequent analyses only present data for the 150-mg dose.[5,6]
- In the responder analysis, 50% of patients receiving berotralstat 150 mg had a ≥70% reduction from baseline in adjusted HAE attack rate compared with 15% for placebo (**Figure 2**).

Figure 2. Exploratory Responder Analysis: Relative Reduction in HAE Attack Rates During Berotralstat Treatment Compared With Prospectively Collected Baseline HAE Attack Rates[a,b]



HAE, hereditary angioedema. [a]An adjusted confirmed HAE attack rate was computed for the determination of the 50% responder endpoint comparing postbaseline attack rates with baseline attack rates. For adjusted confirmed HAE attack rates, the attacks must have been discrete and required treatment or caused functional impairment. The ≥50% responder analysis was prespecified, while the ≥70% responder analysis was performed ad hoc. All P values are nominal for the responder endpoints. [b]Statistical analysis is based on separate logistic regression models with responder status (≥50% or ≥70%) as the outcome variable and treatment and investigator-confirmed baseline attack rate as independent variables.

- The results of the stepwise regression models for rate of investigator-confirmed attacks and the ≥50% and ≥70% responder status and P values for all variables in the final models are shown in **Table 2**. P≤0.05 signifies a predictor of attack rate, ≥50% relative reduction, and ≥70% relative reduction.
- Only study treatment assignment, specifically berotralstat 150 mg, was a strong predictor of response in all 3 models, indicating that assignment to the 150-mg dose was a predictor of attack rate and ≥50% and ≥70% relative reduction in baseline attack rate.
- Age was a significant predictor of ≥70% relative reduction (younger age was associated with a greater chance of ≥70% relative reduction); however, age was not a significant predictor of either ≥50% relative reduction or on-treatment attack rate.

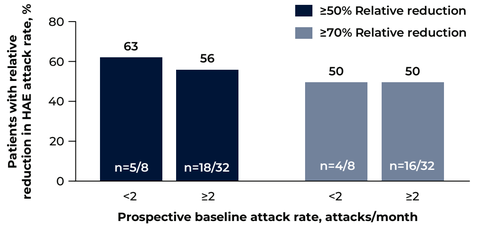
Table 2. Relationship of Baseline Characteristics and the Rate of Investigator-Confirmed Attacks, ≥50% Relative Reduction, and ≥70% Relative Reduction: Final Multivariable Model

	Rate of investigator-confirmed attacks[a]		≥50% responder status[b]		≥70% responder status[b]	
Variable	P value	Significant predictor	P value	Significant predictor	P value	Significant predictor
Treatment group (150 mg)	**<0.001**	**Yes**	**0.006**	**Yes**	**0.005**	**Yes**
Baseline attack rate	**<0.001**	**Yes**	---	---	0.088	No
Prior prophylactic use within 30 days of screening	---	---	0.079	No	0.073	No
Sex	0.146	No	---	---	---	---
Geographic region	0.101	No	---	---	---	---
Prior androgen use	---	---	0.146	No	---	---
Age	---	---	---	---	**0.031**	**Yes**
Weight	---	---	---	---	0.120	No

Bold text indicates a strong correlation. "---" indicates that a variable was not included in the initial run of the multivariable model based on the stepwise selection process; therefore, P values are not calculated. [a]Based on examination of the Aikake information criteria from the corresponding univariate models, continuous weight was used over its categorical version. [b]Based on examination of the univariate models, baseline attack rate and weight category variables were used over their continuous analogs.

- For the primary analysis of the number of attacks occurring during part 1, higher baseline attack rates were predictive of higher attack rates during part 1. For the responder analysis, categorical baseline attack rate was not predictive of the percent reduction in attacks; that is, the likelihood of a 50% reduction in attack rate from 4 to 2 attacks/month or from 1 to 0.5 attack/month was similar.
- Accordingly, the percentage of patients who experienced a ≥50% or ≥70% response to berotralstat 150 mg was similar, regardless of whether baseline attack rate was ≥2 or <2 attacks per month (**Figure 3**).

Figure 3. Percentage of Patients With a Relative Reduction in HAE Attack Rate Stratified by Baseline Attack Rate, 150-mg Berotralstat Treatment Group



HAE, hereditary angioedema.

CONCLUSIONS

1. In the 150-mg berotralstat dose group, 50% of patients had ≥70% reduction in baseline attack rate in part 1 of APeX-2.
2. No patient characteristics were consistent significant predictors of ≥50% response, ≥70% response, and on-study attack rate in a multivariable regression analysis.
3. Baseline attack rate was a predictor of the on-study attack rate but not of ≥50% or ≥70% relative reduction from baseline.
4. Similar percentages of patients on berotralstat 150 mg experienced a ≥50% or ≥70% reduction in attack rate, regardless of whether baseline attack rate was ≥2 or <2 attacks per month.
5. This analysis suggests that berotralstat could become a viable treatment option for any patient with HAE, regardless of baseline characteristics.

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