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Assessment of HAE prophylaxis transition from androgen therapy to berotralstat: A subset analysis of the APeX-S trial

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ABSTRACT

Background: Given the recent approval of oral berotralstat in several countries for hereditary angioedema (HAE) prophylaxis, transition from long-term androgens to berotralstat may occur in clinical practice. The open-label, Phase II APeX-S trial provided an opportunity to assess the safety and effectiveness of berotralstat in patients previously treated with differing durations of androgens and shorter transition periods. Therefore, we examined the safety, effectiveness, and impact on quality of life of berotralstat after prior androgen use in patients from the APeX-S trial. Alanine aminotransferase (ALT) elevations were also examined because of the association with androgen exposure and hepatic function impairment.

Methods: We conducted an analysis of a subset of 39 patients from the APeX-S trial aged $\geq$12 years with HAE due to C1 inhibitor deficiency (HAE-C1-INH) with prior androgen use who discontinued androgen therapy within $<$60 days of receiving berotralstat. Patients received daily berotralstat (150 mg) and were divided into subgroups for this analysis based on time between androgen discontinuation and berotralstat commencement ($<$14 days versus 14 to $<$60 days).

Results: Berotralstat was generally well tolerated, with nasopharyngitis (21%), upper respiratory tract infection (15%), nausea (15%), diarrhea (15%), and abdominal pain (10%) being the most common adverse events occurring in $\geq$10% of the total subset. Only 7/145 (5%) of all APeX-S study patients with a prior history of androgen therapy experienced ALT elevations, 6 of which were grade 3 or 4 toxicities. All 7 patients recovered without sequelae and belonged to the subgroup of patients who transitioned $<$14 days after discontinuing androgens (n = 18). A reduction in monthly attack rate versus Month 1 was observed over 12 months for all patients who transitioned from prior androgen therapy to berotralstat prophylaxis in under 60 days, irrespective of duration of prior androgen therapy or timing of transition (N = 39). Similarly, meaningful patient-reported improvements from both Angioedema Quality of Life Questionnaire and Treatment Satisfaction Questionnaire for Medication scores were achieved, with a sustained benefit shown over the berotralstat treatment period.

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Conclusions: Berotralstat treatment led to sustained HAE symptom control irrespective of duration of prior androgen therapy or timing of transition. Most patients safely transitioned from long-term androgens to berotralstat. Although occurring in a small group of patients, liver-related adverse events following berotralstat treatment may be associated with a shorter androgen washout period, but further research is required to confirm this.

Clinical trial registration: NCT03472040. Retrospectively registered March 21, 2018.

Keywords: Angioedemas, Hereditary, Androgens, Berotralstat, Treatment switching

INTRODUCTION

Hereditary angioedema (HAE) is a genetic disorder affecting an estimated 1 in 50 000 individuals worldwide and is characterized by recurrent, unpredictable angioedema episodes.[1-3] HAE due to C1 inhibitor deficiency (HAE-C1-INH) is caused by detrimental mutations in the gene that codes for C1 esterase inhibitor (C1–INH), a serine protease inhibitor that plays an important role in regulating the kallikrein–bradykinin cascade.[1-3] C1–INH protein deficiency or dysfunction results in heightened kallikrein–bradykinin activity, causing vascular permeability and subsequent swelling.[1,2] HAE attacks can be painful, disfiguring, and reduce an individual's capacity for work, school, and social activities; consequently, patients face a significant lifelong burden.[4,5]

Treatment strategies for patients with HAE-C1-INH include on-demand treatment (administered at the onset of an attack to lessen its duration and severity) and short- and long-term prophylactic treatments to reduce the frequency and severity of attacks.[3,6] There are several therapeutic options for both on-demand and prophylactic treatment; however, availability of the majority of medications is limited in many countries.[6,7] On-demand options include the bradykinin receptor antagonist icatibant, the kallikrein inhibitor ecallantide, plasma (fresh or frozen), and various forms of C1–INH concentrate.[3,6,8] First-line prophylactic options include intravenous plasma-derived C1–INH, subcutaneous plasma-derived C1–INH, the subcutaneous plasma kallikrein inhibitor lanadelumab, and the oral small molecule plasma kallikrein inhibitor berotralstat, which has been recently approved as a first-line prophylactic option for HAE in multiple countries.[3,6,9-12]

Second-line prophylactic options include antifibrinolytics and anabolic androgens (17α-alkylated androgens such as danazol and stanozolol) and are not recommended unless first-line agents are unavailable.[3,6] Antifibrinolytics have not demonstrated significant efficacy as a prophylactic therapy for HAE-C1-INH compared with other preventive medications.[3,6] Androgens have been used for many years (since the 1970s) to prevent and lessen the severity of HAE symptoms, however, they can cause serious dose-related side effects and are contraindicated in several patient populations (such as women and children) because of their androgenic and anabolic effects.[3,6,13] Despite their potential for both short- and long-term toxicity, and the emergence of new efficacious and safe prophylactic therapies, there continues to be widespread use of oral anabolic androgen prophylaxis among patients with HAE, presumably because of limited access to new therapies in many countries.[6,7,14-16]

With the recent approval of berotralstat in several countries, many patients now have another oral option for HAE prophylaxis.[10-12] The safety and efficacy of berotralstat (110 mg and 150 mg doses) were investigated in patients with HAE-C1-INH in the double-blind, placebo-controlled, international, Phase III APeX-2 clinical trial (NCT03485911).[17] Both doses of berotralstat demonstrated a significant reduction in average HAE attack rate compared with placebo at Week 24, which was improved further over 48 and 96 weeks in parts 2 and 3, respectively, of the

study.[17-19] The long-term safety, effectiveness, and impact on quality of life (QoL) of oral berotralstat were further investigated in the open-label international APeX-S study (NCT03472040).[20,21] Patients on previous androgen therapy were included in both the APeX-2 and APeX-S trials.[17,21]

The transition from androgen to berotralstat HAE prophylaxis may occur in routine clinical practice; however, the optimal approach for discontinuing androgens for berotralstat prophylaxis has not been identified. Factors to consider include the timing of transition, dosing schedules, patient-specific preferences and characteristics that may affect transition, and androgen withdrawal. In this report, we detail the safety, effectiveness, and impact on QoL of berotralstat (150 mg) in a subset of patients from the APeX-S study who discontinued androgen therapy within less than 60 days of enrollment (N = 39). Patients were divided into two subgroups based on the time between androgen discontinuation and enrollment in the study because recent discontinuation was relevant for this analysis and an important consideration for patients who transition from prior therapy with androgens to berotralstat HAE prophylaxis in routine clinical practice.

METHODS

Study design and participants

The APeX-S study was an open-label Phase II study of berotralstat in patients aged ≥12 years with HAE-C1-INH conducted in 22 countries.[20] Patients were centrally allocated to receive either 110 mg or 150 mg daily doses of berotralstat; however, on analysis of the results from the APeX-2 trial that demonstrated superior efficacy at 150 mg, patients receiving 110 mg were switched to the 150 mg dose and all subsequently enrolled patients received the 150 mg dose. Patients were required to have access to on-demand medication for acute HAE attacks and to discontinue any androgen therapy for a washout period of at least 7 days (non-US patients) or 28 days (US patients) prior to enrolling in the study. The complete methodology for the APeX-S study has been detailed by Farkas et al.[21]

The APeX-S study 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, 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.[21]

Objectives and outcome measures

The primary objective of the APeX-S study was to evaluate the safety and tolerability of daily dosing of oral berotralstat in patients with HAE-C1-INH. Per protocol, patients who experienced recurrent treatment-emergent liver enzyme elevations >5 times the upper limit of normal (ULN) were required to discontinue the study drug. Alanine aminotransferase (ALT) levels that were ≥3 times the ULN were of interest consistent with the calculation of Hy's law.[22]

The secondary objectives of the study were to assess the effectiveness and impact on QoL of berotralstat. Information on HAE attacks was recorded by patients in a daily journal and confirmed using an algorithm programmed according to predefined criteria outlined in the statistical analysis plan. Due to study design, investigator-confirmed baseline attack rates were not collected for patients enrolled in APeX-S. QoL was assessed at baseline while patients were on prior therapy with androgens and throughout the study using a validated patient-reported angioedema-specific questionnaire, the Angioedema Quality of Life Questionnaire (AE-QoL).[23] The questionnaire includes 17 items and assesses QoL in 4 domains: functioning, fatigue/mood, fear/shame, and nutrition, with a lower total score on the 0–100 scale indicating high QoL.[23] The established minimal clinically important difference (MCID) in total AE-QoL score is a change of 6 points.[23] The Treatment Satisfaction Questionnaire for Medication (TSQM) was used to assess patients' satisfaction with their treatment.[24] The TSQM questionnaire consists of 14 items across four domains: convenience, effectiveness, global satisfaction, and side effects.[24] Scores range from 0 to 100, with higher scores indicating high satisfaction.[24]

Statistical analysis

Results reported herein for the subset of patients from the APeX-S study who received and discontinued prior therapy with androgens within 60 days of berotralstat commencement were based on the final database on June 8, 2022. Descriptive statistics were generated for the subgroups of patients defined below. Means, standard deviations (SD), standard error of the means (SEM), medians, and ranges (minimum [min] and maximum [max]) were generated for continuous endpoints (eg, HAE attack rates and duration of exposure), and the frequency distribution and associated percentages were calculated for categorical variables (eg, treatment-emergent adverse events [TEAEs]). Mean (SD), median, and range (min and max) values for time measurements (eg, age, duration of exposure) were rounded to the nearest whole number. Inferential testing for effectiveness variables was not prespecified in the study protocol. However, changes from baseline, including 95% confidence intervals (CI), have been calculated for AE-QoL and TSQM scores. Descriptive analyses were performed using SAS® version 9.4 for Microsoft Windows (SAS Institute Inc, Cary, NC, USA), and TEAE data were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

RESULTS

Study populations

Overall, 145 patients in the APeX-S study who started on berotralstat 150 mg had a history of previous androgen use prior to study enrollment. Of these, 39 patients discontinued androgen therapy <60 days prior to enrollment and were further categorized as patients who had discontinued androgens <14 days before switching to berotralstat (150 mg; subgroup 1 [n = 18]) and patients who had discontinued androgens ≥14 but <60 before switching to berotralstat (150 mg; subgroup 2 [n = 21]). All patients had received at least one dose of berotralstat (150 mg) treatment and were included in the safety analysis population.

Baseline characteristics

The baseline characteristics of patients included in this analysis are provided in Table 1. The mean (SD) age at study enrollment for all patients who discontinued androgen therapy <60 days prior to enrollment was 44 (12) years; 38.5% (15/39) of

Patient characteristics	Patients from the APeX-S study who received 150 mg of berotralstat daily and discontinued androgen therapy <60 days prior to enrollment		
	Subgroup 1 (<14 days) (n = 18)	Subgroup 2 (≥14 but <60 days) (n = 21)	Total (<60 days) (N = 39)
Age, years			
Mean (SD)	42 (10)	46 (13)	44 (12)
Median (range)	43 (20–55)	48 (17–72)	46 (17–72)
Female, n (%)	9 (50.0)	6 (28.6)	15 (38.5)
Time between androgen discontinuation and berotralstat commencement, days			
Mean (SD)	8 (0.8)	30 (9)	20 (13)
Median (range)	8 (7–9)	30 (14–56)	14 (7–56)
Duration of prior androgen therapy, years			
Mean (SD)	14 (13)	16 (13)	15 (13)
Median (range)	9 (0–44)	10 (0–47)	10 (0–47)
Region, n (%)			
ROW	18 (100)	8 (38.1)	26 (66.7)
USA	0	13 (61.9)	13 (33.3)

Table 1. Baseline patient characteristics. *Abbreviations: ROW, rest of the world; SD, standard deviation; USA, United States of America.*

patients were female. The median (range) time between androgen discontinuation and study entry was 14 (7–56) days overall for the subset, 8 (7–9) days for subgroup 1, and 30 (14–56) days for subgroup 2. The median (range) duration of prior androgen therapy was 10 (<1–47) years for the entire subset; 9 (<1–44) years for subgroup 1, and 10 (<1–47) years for subgroup 2.

Safety and tolerability

Berotralstat exposure

The overall median (range) duration of exposure to berotralstat (150 mg) was 337 (5–1416) days for the 39 patients from the APeX-S study who discontinued androgens <60 days prior to enrollment (361 [15–1170] days for subgroup 1, and 337 [5–1416] days for subgroup 2).

Treatment emergent adverse events

TEAEs were reported in 34/39 (87%) patients in the subset, including 18/18 (100%) patients in subgroup 1, and 16/21 (76%) patients in subgroup 2 (Table 2). The most frequently reported TEAEs occurring in ≥10% of all patients in the subset (Table 3) included nasopharyngitis (21%), upper respiratory tract infection (15%), nausea (15%), diarrhea (15%), and abdominal pain (10%). Drug-related TEAEs occurred in 21/39 (54%) patients in the subset, including 11/18 (61%) patients in subgroup 1, and 10/21 (48%) patients in subgroup 2 (Table 2). Drug-related grade 3 or 4 TEAEs were recorded in 6/39 (15%) patients in the subset (all were liver-related), including 6/18 (33%) patients in subgroup 1, and 0/21 patients in subgroup 2 (Table 2).

Liver function test – Alanine aminotransferase

ALT elevations were recorded in 7/39 (18%) patients (6 of which were Grade 3 or 4 and 1 was Grade 1) in this study; all 7 patients belonged to the subgroup of patients who switched to berotralstat (150 mg) <14 days after discontinuing androgens. Patients were generally asymptomatic, and ALT

	Patients from the APeX-S study who received 150 mg of berotralstat daily and discontinued androgen therapy <60 days prior to enrollment		
	Subgroup 1 (<14 days) (n = 18)	Subgroup 2 (≥14 but <60 days) (n = 21)	Total (<60 days) (N = 39)
AE	**n (%)**	**n (%)**	**n (%)**
Any TEAE	18 (100.0)	16 (76.2)	34 (87.2)
Any drug-related TEAE	11 (61.1)	10 (47.6)	21 (53.8)
Any TESAE	2 (11.1)	1 (4.8)	3 (7.7)
Any drug-related TESAE[a]	1 (5.6)	0	1 (2.6)
Any grade 3 or 4 TEAE	6 (33.3)	1 (4.8)	7 (17.9)
Any drug-related grade 3 or 4 TEAE[b]	6 (33.3)	0	6 (15.4)
Any TEAE leading to interruption of study drug	3 (16.7)	2 (9.5)	5 (12.8)
Any TEAE leading to discontinuation of study drug[c]	6 (33.3)	1 (4.8)	7 (17.9)
Any investigator-identified rash	1 (5.6)	0	1 (2.6)
Any GI abdominal-related TEAE	7 (38.9)	11 (52.4)	18 (46.2)
Any GI abdominal-related TEAE leading to discontinuation	1 (5.6)	1 (4.8)	2 (5.1)

Table 2. Summary of TEAEs. *Abbreviations: ALT, alanine aminotransferase; GI, gastrointestinal; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.* [a]*Berotralstat 150 mg (n = number of patients): ALT elevation (n = 1).* [b]*Berotralstat 150 mg: ALT elevation (n = 4); Hepatic enzyme elevation (n = 1); Liver function test abnormal (n = 1).* [c]*All TEAEs leading to discontinuation of study drug are listed in Supplementary Table 2.*

	Patients from the APeX-S study who received 150 mg of berotralstat daily and discontinued androgen therapy <60 days prior to enrollment		
	Subgroup 1 (<14 days) (n = 18)	Subgroup 2 (≥14 but <60 days) (n = 21)	Total (<60 days) (N = 39)
AE	**n (%)**	**n (%)**	**n (%)**
Any TEAE	18 (100.0)	16 (76.2)	34 (87.2)
Most frequent TEAEs (occurring in ≥10% of total patients in the subset)[a]			
Infections and infestations			
Upper respiratory tract infection	4 (22.2)	2 (9.5)	6 (15.4)
Nasopharyngitis	0	8 (38.1)	8 (20.5)
Gastrointestinal disorders			
Nausea	4 (22.2)	2 (9.5)	6 (15.4)
Abdominal pain	3 (16.7)	1 (4.8)	4 (10.3)
Diarrhea	1 (5.6)	5 (23.8)	6 (15.4)

Table 3. Summary of the most frequent TEAEs occurring in ≥10% of the subset. *Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.* [a]*TEAEs are coded using MedDRA version 19.1. The terms 'abdominal pain,' 'diarrhea,' and 'upper respiratory tract infection' are medical concepts containing multiple preferred terms. 'Abdominal pain' contains the preferred terms 'abdominal pain,' 'abdominal discomfort,' 'abdominal pain upper,' 'abdominal pain lower,' and 'epigastric discomfort.' 'Diarrhea' contains the preferred terms 'diarrhea' and 'feces soft.' 'Upper respiratory tract infection' contains the preferred terms 'upper respiratory tract infection,' 'viral upper respiratory tract infection,' 'respiratory tract infection,' and 'respiratory tract infection viral.' Patients may have experienced the same coded event more than once.*

elevations were transient, not dose-dependent, and none were accompanied by increased bilirubin levels. Of the 7 patients with recorded ALT elevations, all were drug related. No patients met the criteria for Hy's law, and no patients had evidence of hepatitis or any synthetic dysfunction. All seven patients with ALT elevations recovered without sequelae.

A summary of prior androgen use, highest recorded ALT values, and duration of berotralstat exposure for patients with ALT elevations in the total subset is provided in Supplementary Table 1. The median (range) duration of prior androgen therapy in the seven patients with ALT elevations was 17 (1–27) years. The median (range) time between androgen discontinuation and study enrollment was 8 (7–9) days with a median (range) berotralstat exposure prior to increase in ALT levels of 29 (13–253) days. ALT elevations leading to discontinuation were recorded in 5/39 (13%) patients. A summary of all discontinuations due to a TEAE for the total subset (N = 39) is provided in Supplementary Table 2.

Long-term effectiveness

The mean (SD) attack rates for the total subset after 1 month, 6 months, and 12 months of berotralstat treatment were 1.3 (1.9), 0.8 (1.5), and 0.7 (1.0) attacks/month, respectively (0.7 [1.0], 0.6 [0.7], and 0.8 [1.1] attacks/month, respectively, for Subgroup 1; and 1.7 [2.3], 1.0 [1.9], and 0.5 [0.8] attacks/month, respectively, for Subgroup 2). The median (range) attack rates after 1 month, 6 months, and 12 months of berotralstat treatment were 1.0 (0–9), 0.0 (0–7), and 0.0 (0–3) attacks/month, respectively, for the total subset; 0.0 (0–3), 0.5 (0–2), and 0.0 (0–3) attacks/month, respectively, for subgroup 1; and 1.0 (0–9), 0.0 (0–7), and 0.0 (0–2) attacks/month, respectively, for Subgroup 2. Adjusted mean (SEM) and median HAE monthly attack rates over time are provided in Fig. 1a and b.

Quality of life and treatment satisfaction

QoL, as assessed using the AE-QoL questionnaire, improved from baseline to Month 12. Mean (SD) scores at baseline and Month 12 for the AE-QoL total score were 33.7 (18.5) and 15.4 (18.3),

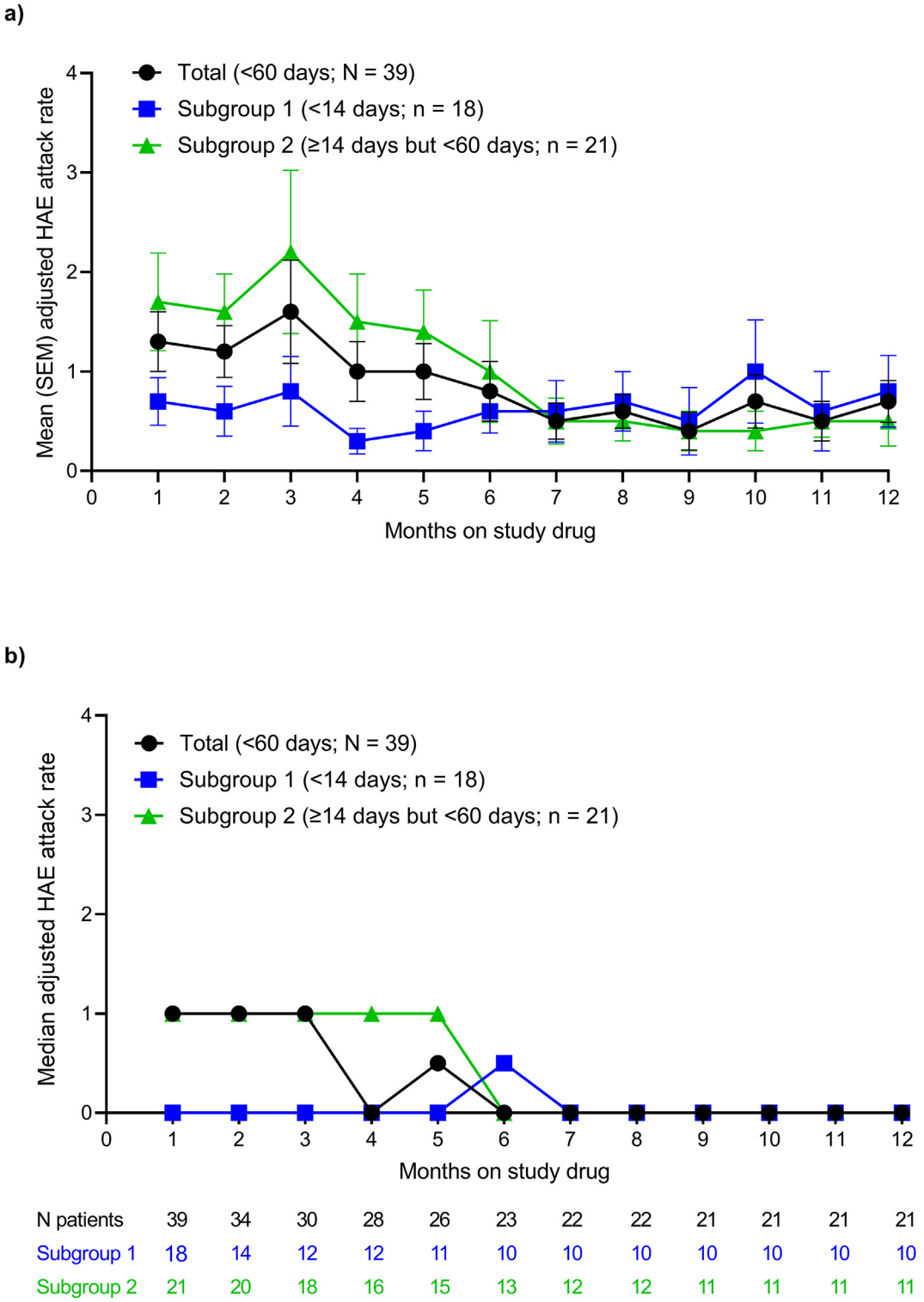

Fig. 1 a) Mean and **b)** median adjusted[a] monthly attack rates over 12 months for the subset of patients from the APeX-S study who switched from androgens to 150 mg of oral berotralstat daily and discontinued androgen therapy <60 days prior to enrollment. [a]An adjusted attack must have been unique (attack begins >24 hours from the end of the prior attack) with a duration of >24 hours if untreated and have included at least 1 symptom of swelling. The adjusted attack rate was defined as the total number of adjusted HAE attacks experienced in the period of interest adjusted for the length of a month (defined as 28 days) and the number of days during that period. Abbreviations: HAE, hereditary angioedema; SEM, standard error of the mean.

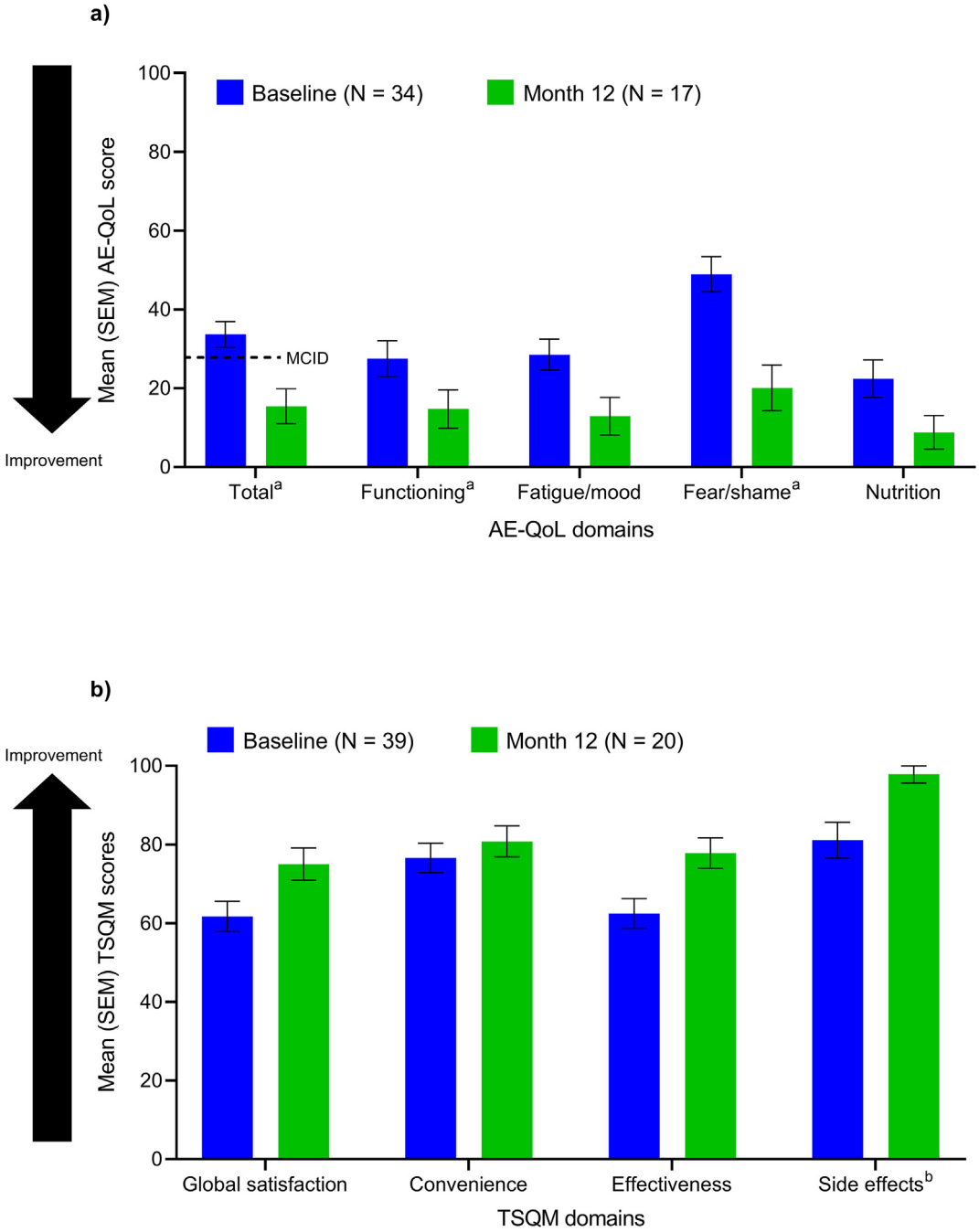

Fig. 2 Baseline and Month 12 values across domains for **a)** mean (SEM) AE-QoL scores and **b)** mean (SEM) TSQM scores for the subset of patients from the APeX-S study who switched from androgens to 150 mg of oral berotralstat daily and discontinued androgen therapy <60 days prior to enrollment. [a]n-value at baseline for total, functioning and fear/shame AE-QoL domains was 33. [b]n-value at baseline for the side effects domain of TSQM was 38. Not all patients completed questionnaires at all timepoints. Patients discontinued from baseline to Month 12 due to lack of efficacy or perceived lack of efficacy, laboratory abnormality or adverse event, withdrawal of consent, or patient decision to continue androgen therapy. Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; MCID, minimum clinically important difference; SEM, standard error of the mean; TSQM, Treatment Satisfaction Questionnaire for Medication.

respectively. Improvements across all four AE-QoL domains were also observed. Mean (SD) scores at baseline and Month 12 were 27.5 (26.0) and 14.7 (20.0), respectively, for the functioning domain, 28.5 (22.9) and 12.9 (19.5), respectively, for the fatigue/mood domain, 48.9 (25.6) and 20.1 (23.8),

respectively, for the fear/shame domain, and 22.4 (27.8) and 8.8 (17.6), respectively, for the nutrition domain. Mean (SEM) values at baseline and Month 12 for all domains are shown in Fig. 2a.

For patients who completed 12 months of berotralstat treatment and completed the AE-QoL questionnaire at Month 12 (n = 17), a clinically meaningful improvement in the AE-QoL total score (change exceeding the MCID) was observed. In these patients, the mean change from baseline to Month 12 was −19.2 (95% CI: −29.0 to −9.4). In the functioning, fatigue/mood, fear/shame, and nutrition domains the mean change from baseline to Month 12 was −16.5 (95% CI: −28.7 to −4.4), −14.4 (95% CI: −26.7 to −2.1), −25.7 (95% CI: −38.9 to −12.6), and −16.9 (95% CI: −30.9 to −2.9), respectively.

Improvements from baseline to Month 12 were also observed across the four patient-reported TSQM domains. The mean (SD) values at baseline and Month 12 were 61.7 (24.0) and 75.0 (18.5), respectively, for global satisfaction, 76.6 (23.2) and 80.8 (17.4), respectively for convenience, 62.5 (23.6) and 77.8 (17.3), respectively, for effectiveness, and 81.1 (28.0) and 97.8 (9.8), respectively for side effects. Mean (SEM) values at baseline and Month 12 for all domains are shown in Fig. 2b.

For patients who completed 12 months of berotralstat treatment and completed the TSQM questionnaire at Month 12 (n = 20), mean change from baseline values were 11.8 (95% CI: −2.4 to 26.0) for global satisfaction, 6.7 (95% CI: −5.0 to 18.3) for convenience, 17.8 (95% CI: 6.4 to 29.1) for effectiveness, and 15.6 (95% CI: 5.0 to 26.2) for side effects.

DISCUSSION

The transition from second-line androgen to first-line berotralstat HAE prophylaxis may occur in routine clinical practice in the case of poor tolerability and/or efficacy of androgens, because of patient and physician preferences, and/or for the convenience and effectiveness of berotralstat. This post hoc subset analysis of the global APeX-S study presented a unique opportunity to assess the long-term safety, effectiveness, and impact on QoL of daily berotralstat (150 mg) in patients who received androgen prophylaxis and discontinued androgens within <60 days of commencing berotralstat therapy. Patients who transitioned from androgen to berotralstat prophylaxis (150 mg) and who have completed the 12 months of berotralstat therapy have experienced sustained HAE symptom control over the duration of berotralstat treatment. The median (range) attack rates were 1.0 (0–9), 0.0 (0–7), and 0.0 (0–3) attacks/month after 1 month, 6 months, and 12 months of berotralstat treatment, respectively, for the total subset. Low attack rates were maintained in subgroup 1. Although attack rates were also low in subgroup 2, there was an observed trend for higher attack rates compared to subgroup 1, which was reduced through 12 months of berotralstat treatment. Despite these early differences, no meaningful difference between the two subgroups can be inferred because of a lack of prespecified statistical analyses. Nonetheless, data from a double-blind study of nine patients suggest that the risk of HAE attack increases quickly after androgen treatment is terminated;[25] therefore, the observed trend in attack rates for Subgroup 2 may be due to the diminishing effects of androgen during the washout period required for this study (median [range] of 30 days [14–56] for subgroup 2), possibly leaving a gap in prophylactic coverage for patients prior to commencing berotralstat therapy.

Overall, patients experienced improvement in QoL (as assessed by the patient-reported AE-QoL) after only 1 month of berotralstat treatment, with improvements continuing throughout the study. The largest changes in QoL for patients from the APeX-S study who transitioned from prior androgen therapy and completed 12 months were observed in the fear/shame and nutrition domains. Patients reported improvements from baseline to Month 12 in global treatment satisfaction, with the largest improvements demonstrated in the side effects and effectiveness domains of the TSQM. QoL and treatment satisfaction are significant unmet needs for patients with HAE, partially because of the high treatment burden associated with some long-term therapies.[3] The ease of administration of the once-daily oral medication berotralstat enables long-term, effective treatment that can improve QoL for many patients with HAE.[17,26]

In this study, berotralstat therapy was generally well tolerated, with no new long-term safety signals observed. The majority of patients (90/145,

62%) with a prior history of androgen therapy remained on berotralstat (150 mg) through 12 months of treatment, but some patients had brief exposure to berotralstat prior to study discontinuation. As such, it is possible that if patients who discontinued the study early had remained on study for longer, the reported incidence of TEAEs may have been higher. However, it is standard practice to report safety for all patients who received at least 1 dose of study drug (safety population). A small number of patients (7/145, 5%) from the full population of patients from the APeX-S study with a prior history of androgen therapy experienced ALT elevations, all of whom transitioned to berotralstat <14 days after discontinuing androgens. As such, 39% (7/18) of patients who transitioned <14 days after discontinuing androgens experienced ALT elevations. Five of these patients discontinued berotralstat due to the ALT elevations.

Examining data from only those patients in this analysis who were enrolled at the South Africa and Poland sites further supports these findings. The South Africa and Poland sites had the highest number of patients with a prior history of androgen use (n = 17) at a single site, 10 of which transitioned in under 60 days. There was also a single physician at each site managing patient transitions, suggesting there may have been more standardized switching methods in place. All patients who transitioned from androgen to berotralstat HAE prophylaxis at these sites discontinued androgen therapy abruptly. At the South Africa and Poland sites, ALT elevations related to study drug occurred in 3 of the 17 patients with a prior history of androgen use, all of whom discontinued androgens <14 days prior to commencing berotralstat and had received androgen therapy for at least 5 years. At the South Africa and Poland sites, two patients discontinued the study because of ALT elevations; however, discontinuation occurred per protocol prior to the observations that ALT elevations were transient. Berotralstat (150 mg) showed effective HAE attack prevention, consistent with what was observed in the total subset.

The mechanism by which androgen exposure may impair hepatic function in some patients is unknown. It has been well established that androgen therapy can cause dose-dependent and duration-dependent hepatotoxicity with subsequent liver injury in patients with HAE-C1-INH and other chronic androgen users.[26–29] Long-term use of anabolic androgens is associated with various forms of hepatotoxicity (possibly due to androgen-induced oxidative stress), including transient liver enzyme elevations, acute cholestatic syndrome, peliosis hepatis, and the development of hepatic adenomas and carcinomas.[29–31] Many of these effects can last for months or even years after androgen discontinuation;[32] therefore, some of the ALT elevations observed in this analysis could be associated with androgen withdrawal rather than as a direct result of berotralstat treatment. Three patients in the APeX-1 study who abruptly discontinued androgens experienced ALT elevations prior to initiation of berotralstat (APeX-1 study [NCT02870972]), further suggesting that some of the ALT elevations in this subset analysis could have been associated with androgen withdrawal. Interestingly, of the 142 patients from APeX-S who started on berotralstat 150 mg and had not received previous androgen therapy, only one patient experienced ALT elevations. Similarly, in the APeX-2 Phase III study, no ALT elevations were experienced by the 52 patients who had not received previous androgen therapy.

Although several studies have documented the adverse effects of prolonged androgen exposure, few studies have illustrated the challenges that may be associated with abrupt transition from androgen HAE prophylaxis to another prophylactic therapy.[33,34] According to a survey of 21 physicians, increased rate and/or severity of HAE attacks and adverse events such as fatigue and mood disturbances that can occur following the discontinuation of androgens are the most common concerns when considering the transition from androgen to another prophylactic therapy for HAE patients.[33] Methods for transitioning from androgen therapy to another HAE prophylactic therapy include abrupt discontinuation, tapering, and overlapping with another prophylactic therapy, and the choice may vary depending on patient and physician preferences. Some healthcare professionals prefer to taper androgen therapy prior to transition to reduce the risk of emergent HAE attacks and androgen withdrawal symptoms.[33] Findings from the recently initiated SHAERPA (Stopping Androgen Treatment in Patients with HAE – Characterization of Reasons

and Protocols and Development of Advice for Patients and Physicians) project should aid further development of consensus guidance on how to transition patients from attenuated androgen treatment to targeted therapies in the future.[34] Our own experience suggests that leaving a longer treatment window without prophylaxis between androgen treatment cessation and initiation of beroteralstat may have an impact on treatment outcomes, and careful planning may be needed to ensure that patient treatment needs are met during this period.

Abrupt discontinuation of androgens immediately prior to the initiation of berotralstat is not recommended by the European Medicines Agency (EMA).[35] Successful initiation of berotralstat in a 29-year-old patient on long-term androgen therapy (oxandrolone 2.5 mg daily) without abrupt discontinuation in the United Kingdom was recently presented as a case report.[36] Berotralstat and androgen therapy were successfully co-administered with a gradual reduction in the dose of androgen to 2.5 mg two days of the week.[36] The patient experienced a reduction in the number of swelling episodes while on berotralstat therapy, minor transient changes in ALT levels, and mild self-limiting gastrointestinal side effects.[36] This method of gradual reduction in the dose of androgen with co-administration of berotralstat was chosen to meet the patient's individual treatment needs.[36]

The subset analysis of patients from the APeX-S study has limitations, including the small sample size (N = 39) and small subgroup sample sizes (n = 18 and n = 21). In addition, other limitations of the APeX-S study are that investigator-confirmed baseline HAE attack rates were not collected for patients and there was no placebo arm to which berotralstat-treated patients could be compared. Furthermore, protocols for switching patients off androgens, which can range from tapering to abrupt discontinuation, may have varied depending on physician and patient preferences and factors, so there were no standardized switching methods in place. Lastly, these data do not offer enough information to confirm if ALT elevations are related to previous androgen use, the recent discontinuation of androgens, or the initiation of berotralstat, and more research is needed. These data may be useful, however, for designing a future study to test exploratory hypotheses.

In conclusion, patients enrolled in the APeX-S study who transitioned from androgen to berotralstat prophylaxis in <60 days achieved high symptom control with improvements in patient-reported QoL and treatment satisfaction observed throughout the study. Consistent trends in HAE attack rate and QoL variables were observed in the full population of patients from the APeX-S study who transitioned from prior androgen therapy to berotralstat (N = 145) as well as the interim analysis of the overall population from the APeX-S study,[21] supporting the overall findings derived from the subset of patients who transitioned from prior androgen therapy to berotralstat prophylaxis in <60 days (N = 39). Berotralstat was generally well tolerated, with only 5% of patients from the full population of patients from the APeX-S study with a prior history of androgen therapy (N = 145) experiencing elevated ALT levels, all of whom transitioned <14 days after discontinuing androgens and recovered without sequelae. Our experience is related to abrupt androgen discontinuation, but strategies to reduce androgen exposure, such as tapering, prior to transition to berotralstat may lower the risk of liver function abnormalities.[33] Also, reducing time without prophylaxis ("washout" period) during androgen discontinuation by avoiding abrupt discontinuation of androgen therapy may need to be considered to ensure a positive initial experience with berotralstat. More research is necessary to confirm this hypothesis. Our current pragmatic clinical approach is to individualize transitions from androgen therapy to berotralstat based on the anticipated acute event frequency during any washout, medical comorbidities, and the availability to monitor patients during transitions.

Abbreviations

AE, adverse event; AE-QoL, Angioedema Quality of Life questionnaire; ALT, alanine aminotransferase; C1-INH, C1 esterase inhibitor; CI, confidence interval; HAE-C1-INH, HAE due to C1 inhibitor deficiency; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GI, gastrointestinal; HAE, hereditary angioedema; MedDRA, Medical Dictionary for Regulatory Activities; MCID, minimal clinically important difference; QoL, quality of life; ROW, rest of the world; SD, standard deviation; SEM, standard error of the mean; SHAERPA, Stopping Androgen

Treatment in Patients with HAE – Characterization of Reasons and Protocols and Development of Advice for Patients and Physicians; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TSQM, Treatment Satisfaction Questionnaire for Medication; ULN, upper limit of normal; USA, United States of America.

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Availability of data and materials
The data that support the findings of this study are available from BioCryst Pharmaceuticals, Inc.

Author's contributions
Phil Collis participated in the design of the study. Jonny G. Peter and Marcin Stobiecki were study investigators. Bhavisha Desai and Dianne Tomita contributed to the analysis of the data. Jonny G. Peter, Marcin Stobiecki, Bhavisha Desai, Dianne Tomita, and Phil Collis participated in the interpretation of data. All authors contributed to the drafting, review, and revision of the manuscript and approved the final draft.

Ethical statement
The APeX-S study 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, 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.

Consent for publication
The authors provide their consent for the publication of the study results.

Declaration of competing interest
Jonny G. Peter has received research funding from BioCryst Pharmaceuticals, Inc. Dianne Tomita and Phil Collis are employees of, and own stocks in, BioCryst Pharmaceuticals, Inc. Bhavisha Desai is a former employee of BioCryst Pharmaceuticals, Inc. Marcin Stobiecki has received research funding from BioCryst Pharmaceuticals, Inc.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100841.

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