ORIGINAL ARTICLE

Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks

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ABSTRACT

BACKGROUND

Approved on-demand treatments for hereditary angioedema attacks need to be administered parenterally, a route of administration that is associated with delays in treatment or withholding of therapy.

METHODS

In this phase 3, double-blind, three-way crossover trial, we randomly assigned participants at least 12 years of age with type 1 or type 2 hereditary angioedema to take up to two oral doses of sebetralstat (300 mg or 600 mg) or placebo for an angioedema attack. The primary end point, assessed in a time-to-event analysis, was the beginning of symptom relief, defined as a rating of "a little better" on the Patient Global Impression of Change scale (ratings range from "much worse" to "much better") at two or more consecutive time points within 12 hours after the first administration of the trial agent. Key secondary end points, assessed in a time-to-event analysis, were a reduction in attack severity (an improved rating on the Patient Global Impression of Severity [PGI-S] scale, with ratings ranging from "none" to "very severe") at two or more consecutive time points within 12 hours and complete attack resolution (a rating of "none" on the PGI-S scale) within 24 hours.

RESULTS

A total of 136 participants were assigned to one of six trial sequences, with 110 treating 264 attacks. The time to the beginning of symptom relief with the 300-mg dose and the 600-mg dose was faster than with placebo ($P<0.001$ and $P=0.001$ for the two comparisons, respectively), with median times of 1.61 hours (interquartile range, 0.78 to 7.04), 1.79 hours (1.02 to 3.79), and 6.72 hours (1.34 to >12), respectively. The time to reduction in the attack severity with the 300-mg dose and the 600-mg dose was faster than with placebo ($P=0.004$ and $P=0.003$), with median times of 9.27 hours (interquartile range, 1.53 to >12), 7.75 hours (2.19 to >12), and more than 12 hours (6.23 to >12). The time to complete resolution was faster with the 300-mg and 600-mg doses than with placebo ($P=0.002$ and $P<0.001$). The percentage of attacks with complete resolution within 24 hours was 42.5% with the 300-mg dose, 49.5% with the 600-mg dose, and 27.4% with placebo. Sebetralstat and placebo had similar safety profiles; no serious adverse events related to the trial agents were reported.

CONCLUSIONS

Oral sebetralstat provided faster times to the beginning of symptom relief, reduction in attack severity, and complete attack resolution than placebo. (Funded by KalVista Pharmaceuticals; KONFIDENT ClinicalTrials.gov number, NCT05259917; EudraCT number, 2021-001226-21.)

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CME

Hereditary angioedema is a rare autosomal dominant genetic disorder that, in most cases, is caused by mutations in *SERPING1* (which encodes C1 inhibitor), resulting in C1 inhibitor deficiency (type 1 disease) or dysfunction (type 2 disease) and subsequent uncontrolled activation of the kallikrein–kinin system.[1,2] Persons with hereditary angioedema have unpredictable and often debilitating episodes of tissue swelling that can be life-threatening if they affect the upper airway.[1-3]

Given the unpredictable potential for rapid progression and anatomic migration of hereditary angioedema attacks, global treatment guidelines recommend that patients consider treating all attacks irrespective of location or severity, always carry sufficient on-demand therapy to treat two attacks, and take treatment as early as possible to arrest the progression of the attack.[1-4] In observational studies and clinical trials, earlier administration of on-demand treatment was associated with a shorter time to the resolution of symptoms, regardless of severity.[5-9]

All first-line on-demand treatment options are administered parenterally, which introduces barriers to compliance with treatment guidelines.[1,2] These impediments include the effort required to transport, store, and prepare the medication; patients' difficulties with administering the drug to themselves; and patients' hesitation in taking the drug because of concern about side effects related to the injection or infusion.[7,10-12] Therefore, many patients delay[6,7,12-16] or withhold[10,14,17,18] on-demand treatment. A safe and effective oral on-demand therapy could reduce much of the burden of parenteral treatment, increasing the likelihood of early treatment and improving clinical outcomes and quality of life.

Although oral treatments have been approved for prophylaxis (most recently, the oral plasma kallikrein inhibitor berotralstat), no oral therapy has been approved for on-demand treatment. Plasma kallikrein and its precursor, prekallikrein, are effective targets for the treatment[19] and prevention[20-22] of hereditary angioedema attacks. Sebetralstat is an oral plasma kallikrein inhibitor in development for the on-demand treatment of hereditary angioedema attacks. In the phase 2 trial, sebetralstat at a dose of 600 mg was rapidly absorbed, resulting in nearly complete inhibition of plasma kallikrein as early as 15 minutes after administration. Sebetralstat treatment resulted in a longer time to the use of conventional treatment for attacks than placebo and was associated with faster relief of symptoms.[23] Sebetralstat was associated with encouraging side-effect and safety profiles.[23,24]

We conducted the phase 3 KONFIDENT trial to assess the efficacy and safety of sebetralstat as compared with placebo for the on-demand treatment of angioedema attacks in participants 12 years of age or older with hereditary angioedema.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN AND OVERSIGHT

KONFIDENT was a double-blind, randomized, placebo-controlled, three-way crossover trial that was conducted to evaluate the efficacy and safety of up to two administrations of sebetralstat (300 mg or 600 mg) as compared with placebo for the on-demand treatment of hereditary angioedema attacks. The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board or ethics committee at each participating institution, and the trial was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice, applicable local regulatory requirements, and the principles of the Declaration of Helsinki. All the participants provided written informed consent.

KalVista Pharmaceuticals (the trial sponsor) participated in the design and conduct of the trial; the collection, management, and interpretation of the data; and the review of the manuscript. Statistical analyses were conducted by the sponsor. The initial draft of the manuscript was prepared by a medical writer funded by the sponsor. Subsequent revisions and the final decision to submit the manuscript for publication were made by the authors, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Eligible participants were 12 years of age or older and had a confirmed diagnosis of type 1 or 2 hereditary angioedema, at least two documented attacks within 3 months before screening or randomization, and access to conventional on-demand therapy. In the participants receiving long-term prophylaxis, the dose and regimen had been stable for at least 3 months before screen-

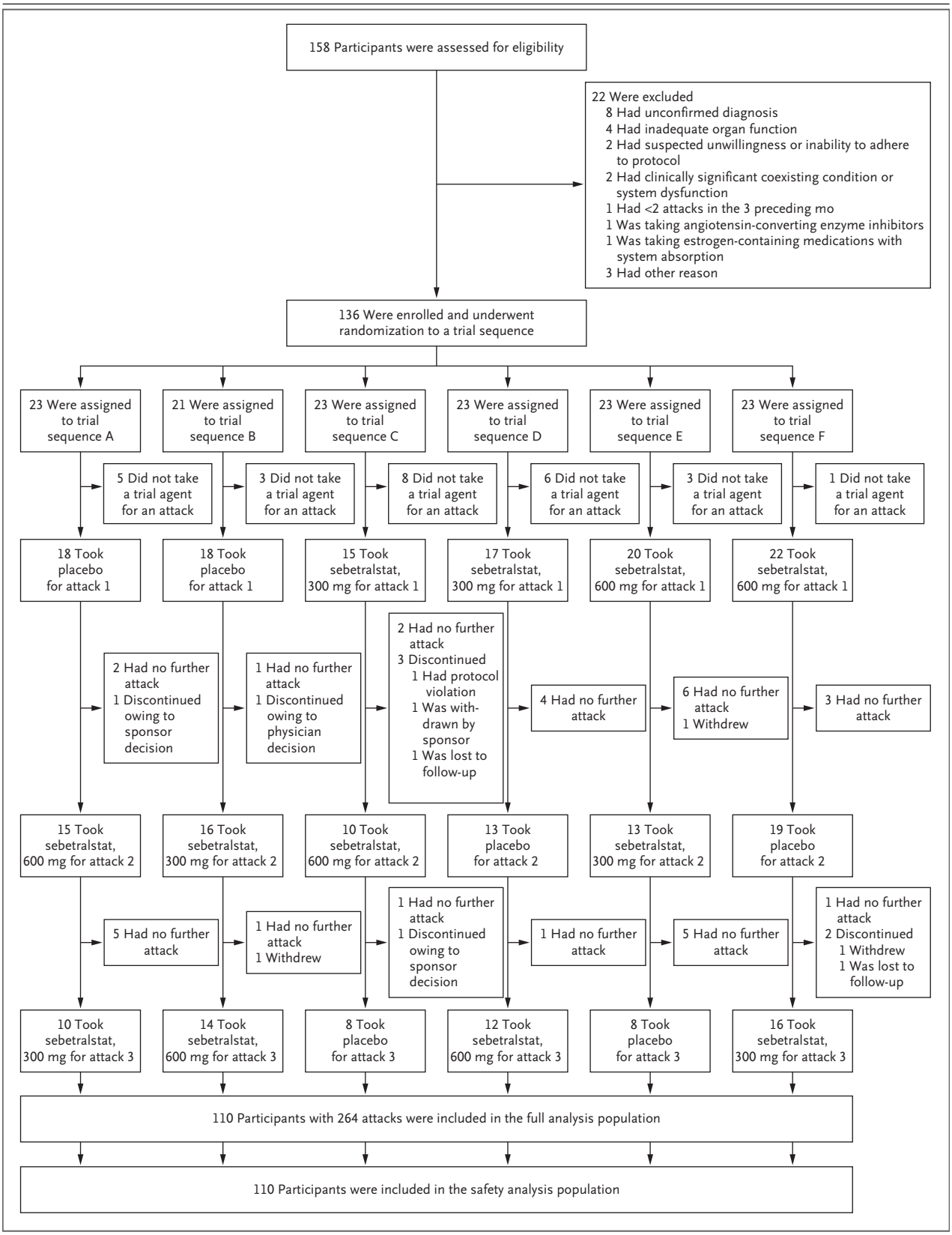


Figure 1 (facing page). Enrollment, Randomization, and Follow-up.

Participants were randomly assigned in a ratio of 1:1:1:1:1:1 to one of six sequences. In each sequence, one or two doses of the first trial agent in the sequence was administered by the participant for the first eligible hereditary angioedema attack, one or two doses of the second trial agent in the sequence was administered for the second eligible attack, and one or two doses of the third trial agent in the sequence was administered for the third eligible attack. Eligible attacks were those considered by the participant to meet the following criteria: the start of the attack could be identified, at least 48 hours had elapsed since the trial agent or conventional treatment was taken for a previous attack, the participant had the ability to enter attack information in an electronic diary during the initial 4 hours after first taking the trial agent, and the attack involved any location and severity at baseline, excluding laryngeal attacks that were considered by the participant to be severe.

ing. Additional details about the inclusion and exclusion criteria are provided in the protocol.

RANDOMIZATION

Participants were randomly assigned in a 1:1:1:1:1:1 ratio to administer sebetralstat at doses of 300 mg and 600 mg and placebo to themselves in one of six sequences (Fig. 1). Randomization was performed with the use of a permuted-block method and was stratified according to the use of long-term prophylaxis at enrollment. Blinding to the sequence assignments was maintained with the use of a double-dummy method.

INTERVENTIONS AND ASSESSMENTS

For each eligible attack and according to sequence assignment, participants were instructed to administer 300 mg of sebetralstat (one 300-mg tablet and one placebo tablet), 600 mg of sebetralstat (two 300-mg tablets), or placebo (two tablets) to themselves as early as possible after the onset of the attack. Participants had the option to administer a second dose of the assigned trial agent at least 3 hours after the first administration. Eligible attacks were those considered by the participant to meet the following criteria: the start of the attack could be identified, at least 48 hours had elapsed since the trial agent or conventional treatment was taken for a previous attack, the participant had the ability to enter attack information in an electronic diary during the initial 4 hours after first taking the trial agent, and the attack involved any location and severity at baseline, excluding laryngeal attacks that were considered by the participant to be severe. Specific guidance for the treatment of laryngeal attacks is described in the Supplementary Appendix (available at NEJM.org). The 48-hour washout period was selected because of the allotted window for the collection of end-point data and the short half-life of sebetralstat.[25]

Information about the attack that was recorded in the electronic diary included location, severity, date and time of onset, the time (or times) that the trial agent was taken, and the use of conventional on-demand treatment, as applicable. Assessments were completed by the participants every 0.5 hours during the first 4 hours after first taking the trial agent, every hour from 5 to 12 hours, every 2 hours from 14 to 24 hours, and every 12 hours from 36 to 48 hours. Safety was assessed primarily according to the occurrence of adverse events, with supplementary information coming from physical examinations, vital signs, electrocardiograms, and laboratory assessments.

EFFICACY END POINTS

The primary end point was the beginning of symptom relief as assessed in a time-to-event analysis. The beginning of symptom relief was defined as a rating of "a little better" on the 7-point Patient Global Impression of Change (PGI-C) scale (ratings range from "much better" to "much worse") at two or more consecutive time points within 12 hours after the first administration of the trial agent.[26] Key secondary end points, assessed in a time-to-event analysis, were a reduction in the severity of the attack, defined as an improved rating on the 5-point Patient Global Impression of Severity (PGI-S) scale (ratings range from "none" to "very severe") at two or more consecutive time points within 12 hours after the first administration, and a complete resolution of the attack, defined as a rating of "none" on the PGI-S scale within 24 hours after the first administration. Prespecified subgroup analyses of the primary and key secondary end points were performed according to age group, use of long-term prophylaxis (yes or no), baseline attack location and severity, number of administrations of the trial agent (1 or 2), and geographic region. Likert scales for the PGI-C

and PGI-S scales have been previously described (Fig. S1).[26]

STATISTICAL ANALYSIS

Efficacy was analyzed in the full analysis population, defined as all the participants who underwent randomization and took the trial agent for at least one attack according to the assigned sequence. The safety analysis population was defined as all the participants who received at least one dose of sebetralstat or placebo. An intention-to-treat analysis with imputation for missing data was performed to assess the sensitivity of the findings to the exclusion of participants who underwent randomization but did not have any attacks during the trial period.

We performed pairwise comparisons of each dose of sebetralstat with placebo. The primary and key secondary end points were assessed with the use of a fixed-sequence, closed-testing procedure that was based on Bonferroni multiplicity adjustment, with a loop-back feature to allow two-way alpha passing. We did not control for multiplicity for other end points. Time-to-event end points were analyzed with the use of the Gehan score transformation.[27] All statistical tests were two-sided with an overall alpha of 0.05.

For the purpose of analysis, treatment failure was defined as the use of conventional treatment before the occurrence of a primary or key secondary end-point event. Therefore, attacks treated with conventional therapy were right-censored at the end of the analysis window. Efficacy end points were censored at 0 hours if the end point could not be derived owing to missing data (e.g., if data from only 1 time point were available). Analyses were conducted under the assumption that missing data were missing at random. Additional details about the statistical analysis, such as the handling of missing data and the calculation of the sample size, are provided in the statistical analysis plan (see the Supplementary Appendix). All analyses were performed with SAS, version 9.4 or higher.

RESULTS

PARTICIPANTS

Between February 23, 2022, and July 30, 2023, a total of 136 participants were recruited from 53 sites across 17 countries and were randomly assigned to one of six trial sequences. Of these participants, 110 administered the assigned trial agent for at least one attack (Fig. 1). Table S1 provides background information on the representativeness of the trial participants with respect to age, sex, and race as reported by the participant. The baseline demographic and disease characteristics of the participants are shown according to trial agent in Table 1 and according to trial sequence in Table S2. The median time since the diagnosis of hereditary angioedema was 12 years (interquartile range, 7 to 22). Twenty-four participants (21.8%) were receiving long-term prophylaxis: berotralstat in 9 (37.5%), lanadelumab in 8 (33.3%), C1 inhibitor replacement in 6 (25.0%), and both berotralstat and C1 inhibitor replacement in 1 (4.2%).

ATTACK CHARACTERISTICS

The trial participants administered at least one dose of sebetralstat or placebo for 264 attacks between February 23, 2022, and December 31, 2023 (Table 2). All 264 attacks were included in the analysis. The distribution of the attack severity at baseline was consistent across the trial agents and according to the use of long-term prophylaxis (Fig. S2 and S3). The median time from the onset of the attack to the first administration of sebetralstat or placebo was 41 minutes (interquartile range, 6 to 140). An optional second administration of the trial agent was used for 34 attacks (39.1%) in the 300-mg group, 37 attacks (39.8%) in the 600-mg group, and 47 attacks (56.0%) in the placebo group (Table S3). Information about most of the attacks was thoroughly recorded in the electronic diary, whereas information about a small percentage of the attacks was insufficient for the assessment of the end points; this percentage was relatively low and balanced across the trial agents (Table S4). Conventional treatment was used within 12 hours after first taking sebetralstat or placebo for 12 attacks (13.8%) in the 300-mg group, 8 attacks (8.6%) in the 600-mg group, and 21 attacks (25.0%) in the placebo group.

EFFICACY END POINTS

The beginning of symptom relief (the primary end point) was reached faster with the 300-mg and 600-mg doses of sebetralstat than with placebo ($P<0.001$ and $P=0.001$ for comparisons with the 300-mg and 600-mg doses, respectively). The median time to the beginning of symptom relief

Table 1. Characteristics of the Participants at Baseline (Full Analysis Population).*

Characteristic	Sebetralstat, 300 mg (N=87)	Sebetralstat, 600 mg (N=93)	Placebo (N=84)	Overall (N=110)
Median age (IQR) — yr	37.0 (25.0–49.0)	39.0 (25.0–49.0)	38.0 (25.0–49.0)	39.5 (25.0–49.0)
Male sex — no. (%)	33 (37.9)	37 (39.8)	29 (34.5)	44 (40.0)
Race — no. (%)†				
White	73 (83.9)	80 (86.0)	73 (86.9)	92 (83.6)
Asian	9 (10.3)	8 (8.6)	7 (8.3)	10 (9.1)
Black	1 (1.1)	0	0	1 (0.9)
Other	0	1 (1.1)	1 (1.2)	1 (0.9)
Not reported	4 (4.6)	4 (4.3)	3 (3.6)	6 (5.5)
Median body-mass index (IQR)‡	26.3 (22.8–31.2)	26.2 (22.9–30.9)	26.2 (22.9–30.8)	26.2 (22.8–31.6)
Geographic region — no. (%)				
Europe	44 (50.6)	49 (52.7)	48 (57.1)	58 (52.7)
United States	27 (31.0)	28 (30.1)	23 (27.4)	34 (30.9)
Asia–Pacific region	16 (18.4)	16 (17.2)	13 (15.5)	18 (16.4)
HAE-C1INH type — no. (%)				
Type 1	79 (90.8)	87 (93.5)	79 (94.0)	101 (91.8)
Type 2	8 (9.2)	6 (6.5)	5 (6.0)	9 (8.2)
Median time since HAE-C1INH diagnosis (IQR) — yr	11 (6–22)	12 (7–22)	12 (7–22)	12 (7–22)
Current treatment regimen — no. (%)				
On-demand treatment only	68 (78.2)	72 (77.4)	66 (78.6)	86 (78.2)
Prophylaxis plus on-demand treatment	19 (21.8)	21 (22.6)	18 (21.4)	24 (21.8)

* The full analysis population comprised participants who administered sebetralstat or placebo to themselves for at least one angioedema attack. Participants may be represented in multiple columns. Percentages may not total 100% because of rounding. HAE-C1INH denotes hereditary angioedema due to C1 inhibitor deficiency and IQR interquartile range.
† Race was reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

was 1.61 hours (interquartile range, 0.78 to 7.04) with the 300-mg dose, 1.79 hours (1.02 to 3.79) with the 600-mg dose, and 6.72 hours (1.34 to >12) with placebo (Fig. 2A). In more than 90% of the attacks in which the beginning of symptom relief occurred with the 300-mg or 600-mg dose, relief occurred without a second administration or before a second administration (Fig. S4).

A reduction in the severity of the attack within 12 hours after the first administration was reached faster with the 300-mg dose and the 600-mg dose than with placebo (P=0.004 and P=0.003, respectively) (Fig. 2B). The median time to a reduction in severity was 9.27 hours (interquartile range, 1.53 to >12) with the 300-mg dose, 7.75 hours (2.19 to >12) with the 600-mg dose, and more than 12 hours (6.23 to >12) with placebo. Complete resolution of the attack was also reached faster with the 300-mg dose and the 600-mg dose than with placebo (P=0.002 and P<0.001, respectively) (Fig. 2C). The percentage of attacks with complete resolution within 24 hours after the first administration was 42.5% with the 300-mg dose of sebetralstat, 49.5% with the 600-mg dose, and 27.4% with placebo.

The results of subgroup analyses according to attack characteristics (Table S5) and participant characteristics (Table S6) suggested that the treatment effects of sebetralstat at doses of 300 mg and 600 mg were consistent with the results in the overall trial population. A subgroup analysis of laryngeal attacks at baseline was not feasible because only eight of these attacks occurred: the 300-mg dose was administered after

Table 2. Characteristics of Attacks for Which One or More Administrations of the Trial Agent Were Taken.

Characteristic	Sebetralstat, 300 mg (N=87)	Sebetralstat, 600 mg (N=93)	Placebo (N=84)	Overall (N=264)
Median score on PGI-S scale at baseline (IQR)*†	2 (1–2)	2 (1–2)	2 (1–2)	2 (1–2)
Rating on PGI-S scale at baseline — no. (%)*				
None	0	0	2 (2.4)	2 (0.8)
Mild	36 (41.4)	41 (44.1)	36 (42.9)	113 (42.8)
Moderate	35 (40.2)	34 (36.6)	33 (39.3)	102 (38.6)
Severe	12 (13.8)	16 (17.2)	10 (11.9)	38 (14.4)
Very severe	2 (2.3)	2 (2.2)	3 (3.6)	7 (2.7)
Missing	2 (2.3)	0	0	2 (0.8)
Median time from attack onset to first administration (IQR) — min	35 (6–130)	41 (5–142)	51 (6–166)	41 (6–140)
Time from attack onset to first administration — no. (%)				
<30 min	40 (46.0)	41 (44.1)	35 (41.7)	116 (43.9)
30 to <60 min	13 (14.9)	9 (9.7)	9 (10.7)	31 (11.7)
≥60 min	33 (37.9)	43 (46.2)	40 (47.6)	116 (43.9)
Missing data	1 (1.1)	0	0	1 (0.4)
Attack location at baseline — no. (%)†‡				
Abdomen	35 (40.2)	42 (45.2)	37 (44.0)	114 (43.2)
Arms, hands, or both	29 (33.3)	26 (28.0)	21 (25.0)	76 (28.8)
Legs, feet, or both	22 (25.3)	23 (24.7)	17 (20.2)	62 (23.5)
Head, face, or neck alone or in combination	9 (10.3)	11 (11.8)	9 (10.7)	29 (11.0)
Torso	5 (5.7)	5 (5.4)	5 (6.0)	15 (5.7)
Genitals	2 (2.3)	4 (4.3)	3 (3.6)	9 (3.4)
Larynx, throat, or both	2 (2.3)	2 (2.2)	4 (4.8)	8 (3.0)
Pooled attack locations — no. (%)‡§				
Mucosal	36 (41.4)	44 (47.3)	40 (47.6)	120 (45.5)
Subcutaneous	49 (56.3)	49 (52.7)	44 (52.4)	142 (53.8)

* A score of 0 on the Patient Global Impression of Severity (PGI-S) scale indicates a rating of none; 1, mild; 2, moderate; 3, severe; and 4, very severe.
† The score on the PGI-S scale and attack location at baseline are missing for two attacks in the 300-mg group.
‡ An attack may be reported in more than one location.
§ Mucosal locations include the abdomen and the larynx, throat, or both. Subcutaneous locations include all other locations.

two such attacks, the 600-mg dose after two, and placebo after four. Several laryngeal attacks were censored because of missing data, which further reduced the number available for analysis. Results of analyses of the intention-to-treat population (with the use of imputation) and analyses of attacks in which data were censored because the participant administered a second dose of the trial agent or conventional treatment suggested that the clinical benefits of sebetralstat were consistent with the results of the primary analysis (Tables S7 and S8).

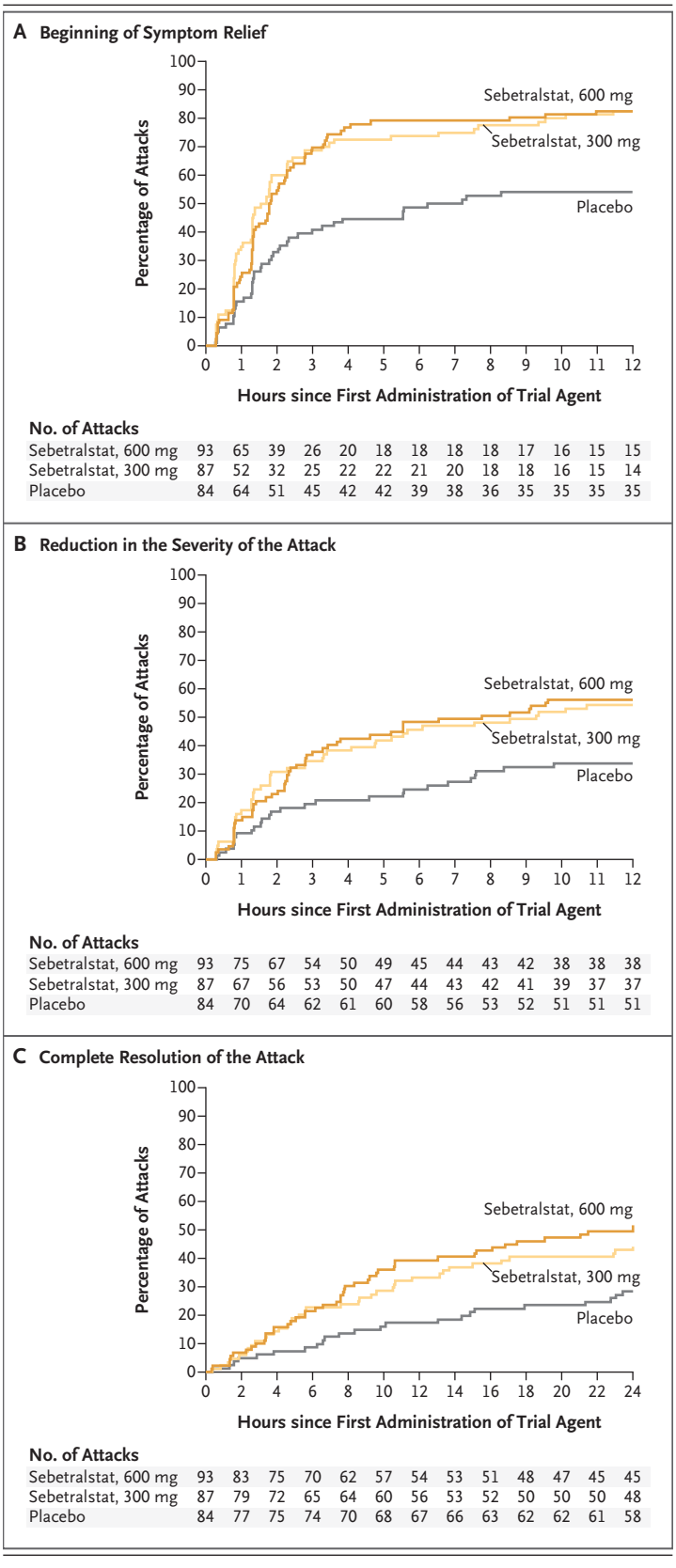
Hazard ratios for the comparison of the 600-mg dose with the 300-mg dose were calculated for the primary and key secondary end points. Results are shown in Figure S5.

SAFETY OUTCOMES

Adverse events occurred in 17 of 86 participants (19.8%) who received 300 mg of sebetralstat, in 14 of 93 (15.1%) who received 600 mg, and in 17 of 83 (20.5%) who received placebo (Table 3 and Table S9). Three serious adverse events were reported; none were related to the trial agent or

Figure 2. Primary and Key Secondary End Points.

Shown in Panel A is the beginning of symptom relief (primary end point) as assessed in a time-to-event analysis. The beginning of symptom relief was defined as a rating of "a little better" on the 7-point Patient Global Impression of Change scale (ratings range from "much better" to "much worse") at two or more consecutive time points within 12 hours after the first administration of sebetralstat or placebo. Also shown are the key secondary end points, assessed in a time-to-event analysis: a reduction in the severity of the attack, defined as an improved rating on the 5-point Patient Global Impression of Severity (PGI-S) scale (ratings range from "none" to "very severe") at two or more consecutive time points within 12 hours after the first administration (Panel B); and a complete resolution of the attack, defined as a rating of "none" on the PGI-S scale within 24 hours after the first administration (Panel C).



occurred within 3 days after sebetralstat or placebo was taken. In the 300-mg group, one case of herniated lumbar vertebrae was reported. In the 600-mg group, one case of anisocoria related to lisdexamfetamine use and one case of exacerbation of a hereditary angioedema attack, in which the patient did not take the trial agent, were reported. Details about adverse events that occurred within 3 days after an administration of sebetralstat or placebo for an attack and adverse events related to the trial agent are shown in Table 3 and Table S10. Physical examination, electrocardiograms, and laboratory assessments, including liver function tests, showed no safety signals.

DISCUSSION

In this phase 3 trial of sebetralstat administered orally at doses of 300 mg or 600 mg for the on-demand treatment of hereditary angioedema attacks, the beginning of symptom relief, a reduction in the severity of the attack, and the complete resolution of the attack occurred significantly faster with each dose level of sebetralstat than with placebo. The observed safety profile of sebetralstat was no different from that of placebo.

Results with each sebetralstat dose level were similar and were consistent across clinically relevant subgroups defined according to age, treatment approach (with or without long-term prophylaxis), and geographic region. The consistency of the effect was also observed in attacks of varying severity and anatomic location (muco-

Table 3. Safety.*

Event	Sebetralstat, 300 mg (N=86)		Sebetralstat, 600 mg (N=93)		Placebo (N=83)	
	no. (%)	*no. of events*	*no. (%)*	*no. of events*	*no. (%)*	*no. of events*
Any adverse event						
Overall	17 (19.8)	20	14 (15.1)	18	17 (20.5)	24
Related to trial agent	2 (2.3)	2	3 (3.2)	4	4 (4.8)	5
Any serious adverse event during treatment†						
Overall	1 (1.2)	1	2 (2.2)	2	0	0
Related to trial agent	0	0	0	0	0	0
Any severe adverse event during treatment‡						
Overall	1 (1.2)	1	0	0	0	0
Related to trial agent	0	0	0	0	0	0
Any adverse event within 3 days after an administration						
Overall	5 (5.8)	5	6 (6.5)	6	10 (12.0)	13
Related to trial agent	2 (2.3)	2	2 (2.2)	2	4 (4.8)	5
Adverse event during treatment that led to trial discontinuation	0	0	0	0	0	0
Adverse event during treatment that led to death	0	0	0	0	0	0
Treatment-related adverse events within 3 days after an administration§						
Gastrointestinal disorders						
Dyspepsia	1 (1.2)	1	0	0	0	0
Nausea	0	0	1 (1.1)	1	1 (1.2)	1
General disorders and administration site conditions						
Fatigue	1 (1.2)	1	0	0	0	0
Nervous system disorders						
Headache	0	0	1 (1.1)	1	1 (1.2)	1
Dysgeusia	0	0	0	0	1 (1.2)	1
Reproductive system and breast disorders						
Menstruation irregular	0	0	0	0	1 (1.2)	1
Skin and subcutaneous tissue disorders						
Rash	0	0	0	0	1 (1.2)	1

* Shown are data for 110 participants who administered the indicated dose of sebetralstat or placebo to themselves for at least one angioedema attack.

† Serious adverse events during treatment were defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or substantial disability or incapacity, was a congenital anomaly or birth defect, or was considered to be an important medical event according to medical and scientific judgment. The three serious adverse events during treatment were the only adverse events that resulted in hospitalization.

‡ Severe adverse events during treatment were defined as adverse events of grade 3 in severity as assessed qualitatively by the investigator or as reported by the participant.

§ Treatment-related adverse events are categorized according to *Medical Dictionary for Regulatory Activities*, version 26.0, system organ class and preferred term.

sal or subcutaneous). A treatment effect in the laryngeal subset of mucosal attacks could not be adequately assessed owing to the small number of events, which was further compounded by missing data. All currently approved on-demand agents that were efficacious in mucosal attacks showed a pattern of clinical benefits in laryngeal attacks.[28] An ongoing, long-term, open-label ex-

tension trial, KONFIDENT-S (ClinicalTrials.gov number, NCT05505916; EudraCT number, 2021-001176-42), is being conducted to assess the safety and efficacy of sebetralstat for on-demand treatment of angioedema attacks, including those involving the larynx.

Comparisons with results from previous randomized clinical trials that assessed injectable on-demand treatments for hereditary angioedema attacks are challenging because of substantial differences in the trial designs and end points.[29] In the most recent trials, patients had to visit trial sites to undergo randomization after an attack became at least moderate in severity,[30,31] site personnel injected the first dose and a second dose if needed (for which the patient had to return to the clinic), and nonandrogenic prophylaxis was not allowed. Of 13 previous randomized, controlled trials that assessed an on-demand treatment in hereditary angioedema, only one trial, which evaluated conestat alfa (recombinant human C1 inhibitor), used a measure similar to that in our trial to assess the time to the beginning of symptom relief — a 7-point treatment-effect questionnaire (ratings range from "much worse" to "much better") that assessed the severity of attack symptoms at affected anatomical locations.[32] The median time to the beginning of symptom relief was 1.5 hours with conestat alfa at a dose of 50 IU per kilogram of body weight (to a maximum of 4200 IU), as compared with 2.5 hours with placebo ($P=0.031$),[32] a finding that was similar to the median times to the beginning of symptom relief with the 300-mg and 600-mg doses of sebetralstat in our trial. In contrast with historical phase 3 trials, our trial aligned with global treatment guidelines by allowing participants to determine when and where to administer therapy. Furthermore, attacks of any severity level (aside from severe laryngeal attacks) were eligible for treatment, and the use of nonandrogenic prophylaxis was allowed.

Although early treatment has been recommended according to treatment guidelines since 2013,[33] observational studies have shown that treatment delays remain common.[6,7,12-16] In support of the concept that oral on-demand treatment may reduce treatment barriers and enable early treatment, the median time to treatment after the onset of an attack was 41 minutes in our trial, with 25% of the participants treating the attack within 6 minutes. In addition, a large percentage of the treated attacks (42.8%) were still mild in severity at the time of treatment, as reported by participants on the PGI-S scale. These data compare favorably to results of observational studies of icatibant, in which the median times to treatment were 1.8 hours and 5.0 hours[13,34] and only 11.6 to 14.6% of the attacks were treated when still mild (or very mild) in severity as defined by measures similar to those used in our trial.[35]

Limitations of this trial include the potential effect of increasingly extended intervals between assessments after the first 4 hours of data collection for each attack, which may have led to the delayed capture of data on participant-reported outcomes. Investigational agents that have shown efficacy as long-term prophylaxis in patients with hereditary angioedema were excluded.[22,36,37] Approximately 19% of the participants who underwent randomization were not included in the safety or efficacy analyses because they did not have an eligible attack during the trial. However, an intention-to-treat analysis that used imputed data for these excluded participants showed results similar to those for the full analysis population.

An oral treatment option for the on-demand treatment of hereditary angioedema attacks is desirable to improve compliance with treatment guidelines and avoid adverse drug reactions related to the injection or infusion. In this phase 3 trial, sebetralstat, an oral plasma kallikrein inhibitor, enabled early treatment of attacks. The administration of sebetralstat for hereditary angioedema attacks led to faster times to symptom relief, reduced severity, and attack resolution than placebo.

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APPENDIX

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