An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover phase 2 trial

Emel Aygören-Pürsün, Andrea Zanichelli*, Danny M Cohn, Mauro Cancian, Roman Hakl, Tamar Kinaciyan, Markus Magerl, Inmaculada Martinez-Saguer, Marcin Stobiecki, Henriette Farkas, Sorena Kiani-Alikhan, Vesna Grivcheva-Panovska, Jonathan A Bernstein, H Henry Li, Hilary J Longhurst, Paul K Audhya, Michael D Smith, Christopher M Yea, Andreas Maetzel, Daniel K Lee, Edward P Feener, Richard Gower, William R Lumry, Aleena Banerji, Marc A Riedl, Marcus Maurer*

Lancet 2023; 401: 458–69

See Comment page 413

*Contributed equally

Department for Children and Adolescents, University Hospital Frankfurt, Frankfurt, Germany (E Aygören-Pürsün MD); Department of Biomedical Sciences for Health, Università degli Studi di Milano, Operative Unit of Medicine, IRCCS Policlinico San Donato, Milan, Italy (A Zanichelli MD); Amsterdam UMC, Department of Vascular Medicine, University of Amsterdam, Amsterdam, Netherlands (D M Cohn MD); Department of Systems Medicine, University Hospital of Padua, Padua, Italy (M Cancian MD); Department of Clinical Immunology and Allergology, St Anne's University Hospital, Brno, Czech Republic (R Hakl PhD); Faculty of Medicine, Masaryk University, Brno, Czech Republic (R Hakl); Department of Dermatology, Medical University of Vienna, Vienna, Austria (T Kinaciyan MD); Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany (M Magerl MD, M Maurer MD); Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany (M Magerl, M Maurer); Haemophilia Centre Rhine Main (HZRM), Mörfelden-Walldorf, Germany (I Martinez-Saguer MD); Department of Clinical and Environmental Allergology, Jagiellonian University Medical

Summary

Background Guidelines recommend effective on-demand therapy for all individuals with hereditary angioedema. We aimed to assess the novel oral plasma kallikrein inhibitor, sebetralstat, which is in development, for on-demand treatment of hereditary angioedema attacks.

Methods In this two-part phase 2 trial, individuals with type 1 or 2 hereditary angioedema aged 18 years or older were recruited from 25 sites, consisting of specialty outpatient centres, across nine countries in Europe and the USA. Individuals were eligible if they had experienced at least three hereditary angioedema attacks in the past 93 days, were not on prophylactic therapy, and had access to and the ability to self-administer conventional attack treatment. In part 1 of the trial, participants were given a single 600 mg open-label oral dose of sebetralstat to assess safety, pharmacokinetics, and pharmacodynamics of the dose. Part 2 was a randomised, double-blind, placebo-controlled, two-sequence, two-period (2×2) crossover trial; participants were randomly assigned (1:1) to either sequence 1, in which they were given a single dose of 600 mg of sebetralstat to treat the first eligible attack and a second dose of placebo to treat the second eligible attack, or sequence 2, in which they were given placebo to treat the first eligible attack and then 600 mg of sebetralstat to treat the second eligible attack. Participants and investigators were masked to treatment assignment. The primary endpoint was time to use of conventional attack treatment within 12 h of study drug administration, which was assessed in all participants who were randomly assigned to treatment and who received study drug for two attacks during part 2 of the study. Safety was assessed in all participants who received at least one dose of study drug, starting in part 1. This study is registered with ClinicalTrials.gov, NCT04208412, and is completed.

Findings Between July 2, 2019, and Dec 8, 2020, 84 individuals were screened and 68 were enrolled in part 1 and received sebetralstat (mean age 38·3 years [SD 13·2], 37 [54%] were female, 31 [46%] were male, 68 [100%] were White). 42 (62%) of 68 participants completed pharmacokinetic assessments. Sebetralstat was rapidly absorbed, with a geometric mean plasma concentration of 501 ng/mL at 15 min. In a subset of participants (n=6), plasma samples obtained from 15 min to 4 h after study drug administration had near-complete protection from ex vivo stimulated generation of plasma kallikrein and cleavage of high-molecular-weight kininogen. In part 2, all 68 participants were randomly assigned to sequence 1 (n=34) or sequence 2 (n=34). 53 (78%) of 68 participants treated two attacks (25 [74%] in the sequence 1 group and 28 [82%] in the sequence 2 group). Time to use of conventional treatment within 12 h of study drug administration was significantly longer with sebetralstat versus placebo (at quartile 1: >12 h [95% CI 9·6 to >12] *vs* 8·0 h [3·8 to >12]; p=0·0010). There were no serious adverse events or adverse event-related discontinuations.

Interpretation Oral administration of sebetralstat was well tolerated and led to rapid suppression of plasma kallikrein activity, resulting in increased time to use of conventional attack treatment and faster symptom relief versus placebo. Based on these results, a phase 3 trial to evaluate the efficacy and safety of two dose levels of sebetralstat in adolescent and adult participants with hereditary angioedema has been initiated (NCT05259917).

Funding KalVista Pharmaceuticals.

Introduction

Hereditary angioedema is a rare and potentially life-threatening genetic disease characterised by unpredictable tissue swelling caused by increased vascular permeability.[1,2] Hereditary angioedema attacks are episodic, with varying frequency and severity within and between individuals. Swelling during these attacks can affect the face, extremities, gastrointestinal tract,

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English before May 14, 2022, assessing treatments for use in the on-demand setting for individuals with hereditary angioedema, using the terms ("on-demand" OR "acute attack*" OR "acute treatment*") AND "hereditary angioedema". No restrictions were applied to the search start date. Our search output did not include any trial data for on-demand therapy presented at scientific congresses because these are not indexed in PubMed. We identified 26 hereditary angioedema clinical studies conducted between 1996 and 2020, of which 22 were clinical trials, and assessed on-demand therapies including plasma-derived or recombinant C1 inhibitors, the kallikrein inhibitor ecallantide, and the bradykinin receptor antagonist icatibant. Outcome measures reported in these trials were heterogeneous, making comparisons across trials difficult. All on-demand treatments assessed were parenteral medications that required intravenous or subcutaneous administration and were delivered by health-care professionals at clinic trial sites within several hours after the onset of an attack. The trials assessed included individuals who had moderate to very severe attacks.

Added value of this study

In this randomised, double-blind, crossover, placebo-controlled trial, we assessed the pharmacokinetics, pharmacodynamics, efficacy, and safety of a single oral dose of sebetralstat. By contrast with previous clinical trials in individuals with hereditary angioedema assessing on-demand treatments, attacks in this trial were to be treated within the first hour of onset, before reaching the severe level (ie, they were mild to moderate) on the Patient Global Impression of Severity (PGI-S) scale, and could be self-administered and treated at home. We found that a single oral dose of sebetralstat resulted in rapid plasma exposure, early and near-complete inhibition of plasma kallikrein generation, and significantly increased the time to use of conventional treatment. Sebetralstat was associated with significantly faster symptom relief, as assessed by the Patient Global Impression of Change, than placebo, and showed improvements in PGI-S and composite visual analogue scale outcomes. There were no serious adverse events or discontinuations due to adverse events. To our knowledge, this is the first peer-reviewed report of an oral therapeutic to treat on-demand attacks in individuals with hereditary angioedema (only one phase 2 trial with a similar approach is currently ongoing [RAPIDe-1; NCT04618211]).

Implications of all the available evidence

Consistent with treatment guidelines that recommend individuals with hereditary angioedema always have access to on-demand treatment and that every attack be treated as early as possible, availability of oral on-demand treatments might help patients overcome the treatment burden related to parenteral administration of approved therapies and could reduce treatment delays and unwanted treatment burden, including adverse events associated with current treatment options.

genitourinary system, and upper airways, which can be life-threatening.[1,2]

Hereditary angioedema types 1 and 2 are caused by autosomal dominant genetic deficiencies of C1 inhibitor expression (type 1; approximately 85% of cases) or function (type 2; approximately 15% of cases).[3–6] The C1 inhibitor acts as the primary physiological inhibitor of factor XIIa and plasma kallikrein, thereby restricting the subsequent generation of the vasoactive peptide bradykinin.[7–12] During a hereditary angioedema attack, elevated concentrations of plasma kallikrein cleave high-molecular-weight kininogen, generating bradykinin, which binds to the bradykinin 2 receptor and leads to a rapid increase in vascular permeability.[13]

Approved therapies for hereditary angioedema comprise on-demand and prophylactic medications. These include the plasma-derived and recombinant C1 inhibitor and bradykinin-2 receptor antagonist icatibant, and plasma kallikrein inhibitors (lanadelumab, ecallantide, and berotralstat). Approved on-demand therapies for acute treatment of hereditary angioedema attacks include only parenteral options: intravenous plasma-derived C1 inhibitor[14,15] and recombinant C1 inhibitor,[16] and the two subcutaneous drugs icatibant[17] and ecallantide.[18] Parenteral administration presents a substantial treatment burden due to the time needed for training, medication preparation and administration, challenges with vascular access, associated pain and discomfort, and infusion-site or injection-site reactions.[18–22]

Sebetralstat (KalVista Pharmaceuticals) is a novel oral plasma kallikrein inhibitor that is in development for the on-demand treatment of hereditary angioedema attacks. A phase 1 trial showed that sebetralstat is rapidly absorbed and reached maximum plasma concentration within 1 h.[23] Plasma concentrations necessary for near-complete plasma kallikrein inhibition (>90%) were reached within 20–30 min and maintained for up to 8 h. In this phase 2 trial, we investigated the pharmacokinetic and pharmacodynamic characteristics of a single oral dose of 600 mg of sebetralstat and its efficacy and safety in treating hereditary angioedema attacks.

Methods

Study design and participants

This phase 2 study was run in two parts: in part 1, we assessed the safety, pharmacokinetics, and pharmacodynamics of a single dose of sebetralstat, and in part 2, we assessed the efficacy, safety, and tolerability of a single dose of sebetralstat in an outpatient, randomised,

College, Krakow, Poland (M Stobiecki MD); **Hungarian Angioedema Center of Reference and Excellence, Department of Internal Medicine and Haematology, Semmelweis University, Budapest, Hungary** (H Farkas MD); **Barts Health NHS Trust, Department of Immunology, GA²LEN/HAEi Angioedema Centre of Reference and Excellence, London, UK** (S Kiani-Alikhan MB-PhD); **PHI University Clinic of Dermatology, School of Medicine, University Saints Cyril and Methodius, Skopje, North Macedonia** (V Grivcheva-Panovska MD); **University of Cincinnati College of Medicine and Bernstein Clinical Research Center, Cincinnati, OH, USA** (J A Bernstein MD); **Institute for Asthma and Allergy, Chevy Chase, MD, USA** (H H Li MD); **Department of Immunology, Auckland District Health Board and University of Auckland, Auckland, New Zealand** (H J Longhurst MD); **KalVista Pharmaceuticals, Salisbury, UK** (C M Yea PhD); **KalVista Pharmaceuticals, Cambridge, MA, USA** (P K Audhya MD, M D Smith PharmD, A Maetzel MD, D K Lee BA, E P Feener PhD); **Institute of Health Policy, Management & Evaluation, University of Toronto, ON, Canada** (A Maetzel); **Marycliff Clinical Research, Spokane, WA, USA** (R Gower MD); **AARA Research Center, Dallas, TX, USA** (W R Lumry MD); **Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, USA** (A Banerji MD); **Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA, USA** (M A Riedl MD)

Correspondence to:
Dr Marcus Maurer, Institute of Allergology, Charité – Universitätsmedizin, Berlin 12203, Germany
marcus.maurer@charite.de

double-blind, placebo-controlled, two-sequence, two-period (2×2) crossover trial.

Participants were recruited from 25 sites consisting of specialty outpatient centres in nine countries in Europe and the USA (appendix p 13). Adults (aged ≥18 years) with a confirmed diagnosis of hereditary angioedema type 1 or 2, who had experienced at least three attacks in the past 93 days, were not on prophylactic therapy, and had access to and ability to self-administer conventional attack treatment (ie, plasma-derived C1 inhibitor or recombinant C1 inhibitor, or icatibant) were eligible to participate in the trial. Laryngeal or facial attacks (which might be difficult to distinguish from laryngeal attacks) were ineligible for treatment due to the possibility of treating these potentially life-threatening attacks with placebo (appendix p 4). Only patients with adequate organ function (eg, adequate hepatic and renal function) were included, and patients receiving angiotensin-converting enzyme inhibitors or strong cytochrome P450 3A4 or 2C9 inhibitors and inducers were excluded. Full inclusion and exclusion criteria are in the appendix (pp 3–4).

See Online for appendix

The trial was approved by the relevant institutional review board or ethics committee, followed good clinical practice guidelines, observed the Declaration of Helsinki, and followed the guidance of the International Conference on Harmonisation. All participants provided written informed consent.

Several protocol amendments were made as a result of the COVID-19 pandemic (the initial amendment was made on June 5, 2020, before full recruitment) that were as follows: new participants did not undergo pharmacokinetics and pharmacodynamics assessments in part 1, only safety observations; all sites were directed to act in accordance with COVID-19-related recommendations by their governing authorities and country and local restrictions; and participants had the option to postpone trial activity under specific scenarios that included if the patient did not want to visit the study site due to the risk of COVID-19 or if the study site was closed because the clinical staff were reassigned during periods of high SARS-CoV-2 transmission.

Randomisation and masking

In part 1 of the study, all participants were given an open-label, single oral dose of 600 mg sebetralstat. In part 2, participants were randomly assigned (1:1) to receive study drug in one of two sequences: sequence 1, in which they were to self-administer a single dose of 600 mg of sebetralstat to treat the first eligible hereditary angioedema attack, and a dose of matched placebo to treat the second eligible attack; or sequence 2, in which they were to self-administer placebo to treat the first eligible attack, and a single dose of 600 mg of sebetralstat to treat their second eligible attack. The randomisation scheme was generated by an independent statistician using computer software (SAS statistical software version 9.3) that incorporated a standard procedure for generating randomisation numbers. Part 2 of the trial was done in a double-blind manner, with participants, investigators, and all treating staff masked to treatment allocation. Masking was achieved with a matched placebo, which had an identical appearance to the active drug, and so kits were distributed and self-administered without investigators or participants knowing which kit contained which sequence. The unblinded members of the trial were those who packaged the study drug, the individual who oversaw this effort, and the unblinded statistician who generated the scheme. The blinding was not to be broken except for a medical emergency or regulatory requirement. For a medical emergency, the investigator would determine if unblinded information was necessary for a patient's immediate management. Unblinding of any trial participant would be reported as a major protocol deviation. No treatment was unblinded for individual participants until the entire trial was unblinded.

Procedures

In part 1, participants were given a single oral dose of 600 mg of sebetralstat within 28 days of their screening visit. Assessment of vital signs and safety laboratory tests were done before and at 1 h and 4 h after study drug administration. Plasma samples were taken during part 1 before, every 15 min for the first hour, and at 1·5, 2, 3, and 4 h after study drug administration. Pharmacokinetic parameters including maximum concentration in plasma (C_{max}), the time to reach C_{max} in plasma (T_{max}), and the area under the curve (AUC) from time 0 to the last sample at 4 h ($AUC_{0-4\ h}$) were determined. For pharmacodynamic analyses, plasma samples were obtained before and after study drug administration from a randomly selected cohort of participants from three clinical sites (Berlin, Germany; Morfelden-Waldorf, Germany; and Budapest, Hungary) in part 1. Undiluted samples were stimulated with 6·25 µg/mL dextran sulfate (Sigma Aldrich) at 0°C for 17 min. Plasma samples were heated to 95°C for 10 min in Laemmli buffer containing β-mercaptoethanol and separated by capillary electrophoresis (WES system, ProteinSimple, Santa Clara, CA, USA). Prekallikrein and plasma kallikrein were detected with immunoassay using Ab44392 antibody (Abcam, Waltham, MA, USA) and horseradish peroxidase-conjugated secondary antibody. Prekallikrein and plasma kallikrein were quantified from chemiluminescence intensities using Compass for Simple Western software (version 4.0.0, ProteinSimple) and compared with high-molecular-weight kininogen and cleaved high-molecular-weight kininogen concentrations, as described previously.[24]

In part 2, participants were assigned to their respective sequence groups (sequence 1 or sequence 2) and a minimum 48-h washout period was required between each eligible attack and, therefore, each dose of study drug. Participants were required to identify the start of the hereditary angioedema attack and notify the trial

physician or qualified designee via telephone with a description of the attack. After telephone validation of attack eligibility, participants were advised to administer the study drug within 1 h of onset and before the attack reached a severe level, as defined on the Patient Global Impression of Severity (PGI-S) scale. Participants were asked to record the time of onset of an eligible attack, its location, severity, and symptoms. Primary attack locations were categorised as abdominal, arms or legs, genitals, or other. Participants recorded the effect of treatment and onset of symptom relief using the 7-point Patient Global Impression of Change (PGI-C) scale and a set of three 100-mm visual analogue scales (VAS) assessing abdominal pain, skin pain, and skin swelling. Attack severity was assessed using the 5-point PGI-S. Assessments were recorded every 30 min for the first 4 h, every hour from 4 h to 12 h, every 3 hours from 12 h to 24 h, and once at 36 h and 48 h after study drug administration. Conventional treatment was permitted 4 h (or earlier if warranted) after administration of study drug if attack symptoms were deemed severe enough by the participant to require additional treatment or were ineligible for study drug treatment, or immediately if the attack was associated with development of laryngeal or facial symptoms. If conventional treatment was used, participants did assessments every 30 min for 4 h after the first administration of conventional attack treatment. Details of these measurements are in the appendix (p 5). Adverse event reporting, documentation of vital signs, and laboratory measurements were completed at the visits that were scheduled to occur as soon as practical (within 7 days) following the first and second home-treated attacks. All adverse events were classified using version 22.0 of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. An adverse event was classified as severe if the event was intolerable, necessitated additional therapy or alteration of therapy, and interfered with the participant's daily activities. Adverse event grading criteria are provided in the appendix (p 7). At the visit following the first attack, participants received the second dose of their sequence. After the second attack, participants resumed their standard treatment and medical care for hereditary angioedema. Details of clinical assessments are in the appendix (p 6).

Outcomes

The primary endpoint was the time to use of conventional attack treatment within 12 h after study drug administration. The secondary endpoints were time to symptom relief, defined as the hereditary angioedema attack being rated at least "a little better" on the PGI-C for two consecutive timepoints, within 12 h of study drug administration; time to symptom relief, defined as at least 50% reduction from baseline in the composite VAS score (the arithmetic mean of all three VAS measurements: abdominal pain, skin pain, and skin swelling) for at least three consecutive timepoints within 12 h of study drug administration; time to either use of conventional attack treatment or worsening of attack severity by one level or more on the PGI-S within 12 h of study drug administration; and proportion of attacks associated with either use of conventional attack treatment or worsening of attack severity by one level or more on the PGI-S within 12 h of study drug administration.

Prespecified exploratory endpoints included primary and secondary endpoints measured within 24 h of study drug administration; proportion of attacks for which conventional attack treatment was taken within 12 and 24 h of study drug administration; proportion of attacks rated at least "a little better" on the PGI-C scale for two consecutive timepoints within 12 and 24 h of study drug administration; median time to attack being rated at least "better" as defined by the PGI-C within 24 h of study drug administration; median time to attack being rated at least "a little worse" on the PGI-C for two consecutive timepoints or use of conventional attack treatment, whichever happened first, within 12 or 24 h of study drug administration; median time to attack being

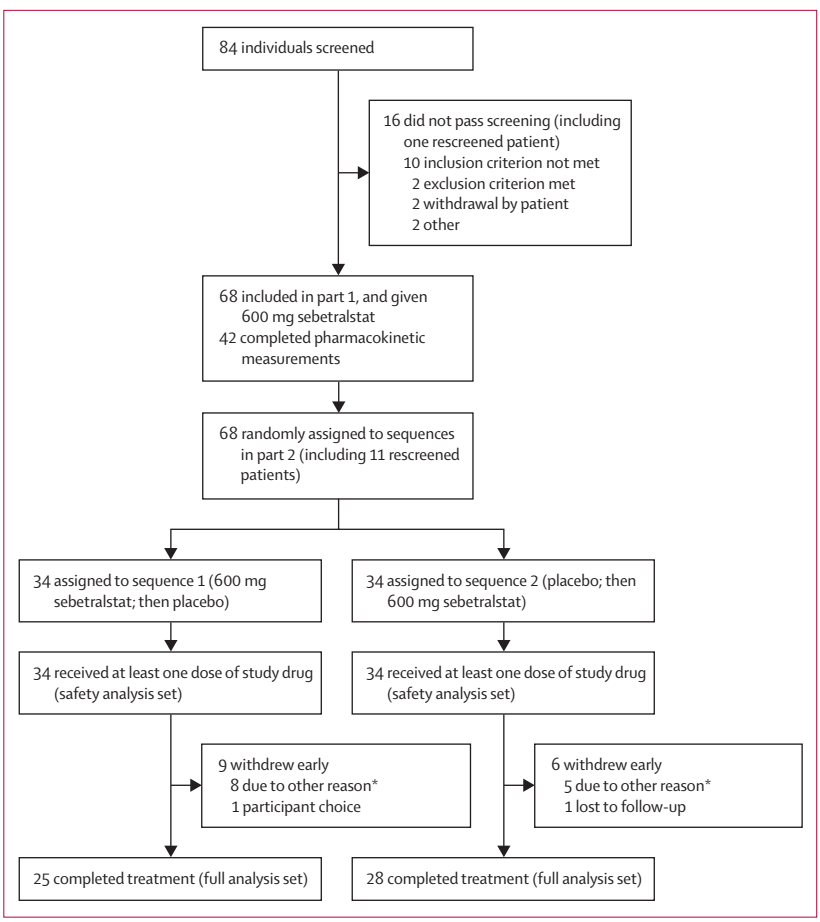

Figure 1: **Trial profile**
*Patients with reason for withdrawal given as "other" were withdrawn due to early discontinuation of the trial after a sufficient number of patients had completed treatment of two attacks.

rated at least "a little worse" on the PGI-C for two consecutive timepoints within 12 or 24 h of study drug administration; proportion of attacks that were stable or improved within 12 or 24 h of study drug administration; proportion of attacks that resulted in symptom relief on VAS within 12 and 24 h of study drug administration; median time to attack resolution, defined as a PGI-S rating of "none", within 12 and 24 h of study drug administration; proportion of attacks that had attack resolution, defined as a PGI-S rating of "none", within 12 and 24 h of study drug administration; proportion of attacks that improved by 1 level or more on the PGI-S from baseline within 12 or 24 h of study drug administration; and median time to improvement by 1 level or more on the PGI-S from baseline within 12 or 24 h of study drug administration. An analysis was performed post hoc to assess the proportion and time to symptom relief defined by a 50% reduction of the VAS with the highest score at baseline (ie, the index VAS) for three consecutive timepoints within 12 h of study drug and individual VAS components.

The following safety-related assessments were performed during the trial: adverse events, including their seriousness, severity, and association with study drug; laboratory assessments; vital signs; complete physical examinations; electrocardiogram; and monitoring of concomitant medication use. Any clinically significant findings were to be recorded as adverse events.

	Part 1 study cohort (N=68)	Part 2 study cohort	
		Sequence 1 group (sebetralstat then placebo; n=34)	Sequence 2 group (placebo then sebetralstat; n=34)
Age, years	38·3 (13·2)	41·0 (13·0)	35·5 (13·1)
Sex			
Female	37 (54%)	22 (65%)	15 (44%)
Male	31 (46%)	12 (35%)	19 (56%)
Race			
White	68 (100%)	34 (100%)	34 (100%)
Other race	0	0	0
Country of residence			
Austria	4 (6%)	3 (9%)	1 (3%)
Czech Republic	9 (13%)	4 (12%)	5 (15%)
Germany	14 (21%)	6 (18%)	8 (24%)
Hungary	3 (4%)	1 (3%)	2 (6%)
Italy	12 (18%)	7 (21%)	5 (15%)
Macedonia	3 (4%)	1 (3%)	2 (6%)
Netherlands	5 (7%)	3 (9%)	2 (6%)
Poland	4 (6%)	2 (6%)	2 (6%)
UK	8 (12%)	4 (12%)	4 (12%)
USA	6 (9%)	3 (9%)	3 (9%)
BMI, kg/m²	27·3 (5·5)	27·2 (5·7)	27·3 (5·3)
Time since diagnosis, years	19·9 (13·4)	22·7 (14·0)	17·1 (12·3)

Data are mean (SD) or n (%).

Table 1: **Baseline characteristics (safety analysis set)**

Statistical analysis

The planned sample size was 60 participants randomly assigned to treatment sequences to determine the outcomes of 50 participants with complete trial data (ie, treatment of two hereditary angioedema attacks), providing at least 90% power to show the difference between sebetralstat and placebo for the primary endpoint.

We did the primary analysis using the full analysis set, which was defined as all participants who were randomly assigned to a treatment sequence and received study drug for two attacks in part 2 of the study. The safety analysis set included all participants who received at least one dose of study drug, starting with part 1. The pharmacokinetic analysis set included all participants who completed the pharmacokinetic measurements in part 1. We used a one-way ANOVA with Fisher's least significant difference test for the pharmacodynamic analysis. We used Gehan's generalised Wilcoxon test, as proposed by Feingold and Gillespie,[25] an extension of the Wilcoxon rank sum test, to do a non-parametric analysis of time-to-event data (appendix p 8). This is a rank-based approach that is appropriate for crossover time-to-event data because it provides a test statistic in the presence of censoring, including when the median is censored. We used Prescott's test to compare proportions between treatments. All these tests were prespecified. We summarised all patient-reported outcome measures over time and explored them using AUC calculations. We did no imputations for missing values (eg, missed assessments during sleep). Outcomes reported after conventional attack treatment were excluded from analyses. We plotted time-to-event data using standard Kaplan-Meier methods.

We considered p values of less than 0·05 to be significant. The statistical analysis plan was developed in compliance with the International Conference on Harmonisation E9 document *Statistical Principles for Clinical Trials*, and all analyses in part 2 were done using SAS (version 9.3). This trial is registered with ClinicalTrials.gov, NCT04208412.

Role of the funding source

The sponsor participated in the design of the trial, trial conduct, data collection, data management, data analysis, data interpretation, and review of the manuscript.

Results

Between July 2, 2019, and Dec 8, 2020, 84 adults with hereditary angioedema were screened, of whom 68 were enrolled and given oral 600 mg sebetralstat in the clinic in part 1. 42 (62%) of 68 participants who received sebetralstat in part 1 completed pharmacokinetic assessments (figure 1); the remaining 26 participants did

not attend clinics for measurements due to the COVID-19 pandemic (appendix p 9). Six (14%) of 42 participants were randomly selected and their plasma samples analysed for the pharmacodynamics of dosed sebetralstat. All 68 participants continued to part 2 and were randomly assigned to sequence 1 (sebetralstat–placebo; n=34) or sequence 2 (placebo–sebetralstat; n=34; figure 1). 53 participants completed the trial, having and treating two hereditary angioedema attacks during part 2 of the study: 25 (74%) in the sequence 1 group and 28 (82%) in the sequence 2 group (full analysis set). 15 participants did not complete part 2 of the trial, of whom 13 were withdrawn due to early discontinuation of the study after a sufficient number of participants had completed treatment of two attacks, one withdrew consent, and one was lost to follow-up. 37 (54%) of 68 participants were female, 31 (46%) were male, all were White (68 [100%]), with a mean age of 38·3 years (SD 13·2), a mean time since diagnosis of 19·9 years (13·4; table 1), and an arithmetic mean of 1·5 (0·76) attacks per month (range 1·0–4·7). There were no clinically meaningful differences in the demographics or baseline characteristics between the sequence groups.

113 attacks were treated during the trial, and most were rated as mild (57 [50%]) or moderate (51 [45%]) at onset (appendix p 15). At the time of attack onset, 30 (27%) attacks were abdominal, 77 (68%) were peripheral (included arms, legs, genitals, or other areas), and six (5%) were in both anatomical regions. 109 (97%) of 113 attacks were treated within 1 h of onset. The median time from recognition of attack onset to oral administration of study drug was 30 min (IQR 21–50; including the time needed to contact the study physician to verify attack eligibility; appendix p 10). Median elapsed time between the first and second attack was 23 days (range 5–140; IQR 13–45).

In part 1 of the study, sebetralstat was rapidly absorbed after oral administration, with a geometric mean plasma concentration of 501 ng/mL at 15 min (n=42; appendix p 11). Plasma levels of sebetralstat reached maximum values (geometric mean C_{max} 6080 ng/mL) with an observed median T_{max} of 1·00 h (range 0·433–3·00).

Among the six participants who were randomly selected as representative of the cohort of samples previously studied for plasma kallikrein activity,[24] dextran sulfate stimulation of pre-dose plasma decreased prekallikrein by more than 85% and high-molecular-weight kininogen by more than 99% compared with unstimulated plasma (figure 2A). In post-dose plasma samples, prekallikrein concentrations after dextran sulfate stimulation were similar to the prekallikrein concentrations in unstimulated pre-dose plasma samples. Sebetralstat reduced dextran sulfate-stimulated generation of plasma kallikrein by 65% at 0·25 h and by more than 90% between 0·5 h and 4 h after study drug administration compared with dextran sulfate-stimulated pre-dose plasma (p<0·0001; figure 2B). Inhibition of dextran sulfate-stimulated prekallikrein activation with sebetralstat was associated with near-complete protection of high-molecular-weight kininogen cleavage by more than 90% between 0·5 h and 4 h after study drug administration.

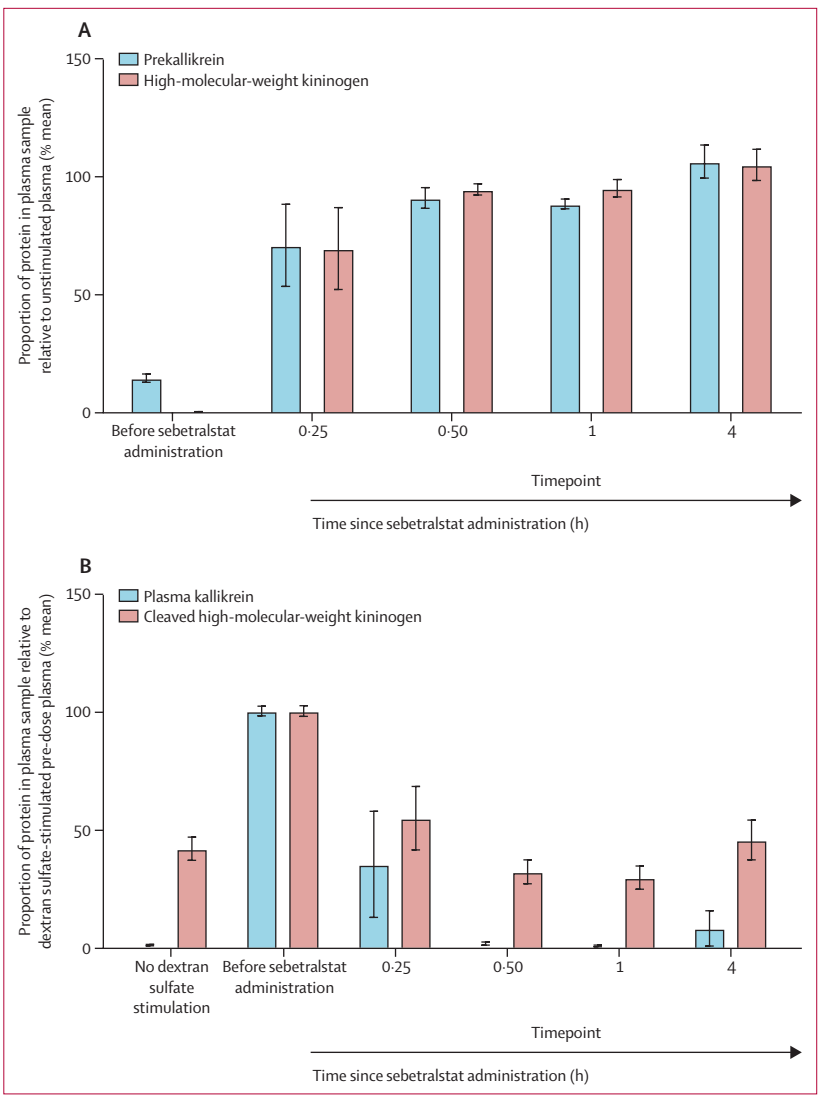

Figure 2: **Effect of orally administered sebetralstat on kallikrein-kinin system components in dextran sulfate-stimulated hereditary angioedema plasma**
Bar graphs show proportion of prekallikrein and high-molecular-weight kininogen in plasma samples relative to unstimulated plasma (A) or plasma kallikrein and cleaved high-molecular-weight kininogen relative to dextran sulfate-stimulated pre-dose samples (B) from six patients with hereditary angioedema (each individual sample is the mean of duplicate tests). Error bars show the standard error of the mean (SEM). All post-dose values were significant relative to before study drug administration (p<0·0001).

The primary endpoint of the trial was met, with sebetralstat significantly increasing the time to use of conventional attack treatment within 12 h of study drug administration compared with placebo (first quartile [Q1]: >12 h [95% CI 9·6 to >12] with sebetralstat *vs* 8·0 h [3·8 to >12] with placebo [median not reached]; p=0·0010; table 2).

This increase in time to use of conventional attack treatment was maintained over 24 h (Q1 >24 h [95% CI 9·5 to >24] with sebetralstat *vs* Q1 8·0 h [3·8–16·5] with

	Attacks treated with sebetralstat (n=53)	Attacks treated with placebo (n=53)	p value
Time to use of conventional attack treatment, h			
Within 12 h (primary endpoint)	..	..	0·0010*
Quartile 1	>12 (9·5 to >12)	8·0 (3·8 to >12)	..
Median	>12 (>12 to >12)	>12 (>12 to >12)	..
Quartile 3	>12 (>12 to >12)	>12 (>12 to >12)	..
Within 24 h (exploratory endpoint)	..	..	0·0005*
Quartile 1	>24 (9·5 to >24)	8·0 (3·8 to 16·5)	..
Median	>24 (>24 to >24)	>24 (15·9 to >24)	..
Quartile 3	>24 (>24 to >24)	>24 (>24 to >24)	..
Time to attack being rated at least "a little better" on the PGI-C for two consecutive timepoints, h			
Within 12 h (secondary endpoint)	..	..	<0·0001*
Quartile 1	0·6 (0·6 to 1·5)	2·0 (0·6 to 4·0)	..
Median	1·6 (1·5 to 3·0)	9·0 (4·0 to >12)	..
Quartile 3	5·0 (3·0 to 12·0)	>12 (>12 to >12)	..
Within 24 h (exploratory endpoint)	..	..	<0·0001*
Quartile 1	0·6 (0·6 to 1·5)	2·0 (0·6 to 4·0)	..
Median	1·6 (1·5 to 3·0)	9·0 (4·0 to 17·2)	..
Quartile 3	5·0 (3·0 to 12·0)	24·0 (17·2 to 24·0)	..
Proportion of attacks associated with either use of conventional attack treatment or worsened attack severity by 1 level or more on the PGI-S, n (%)			
Within 12 h (secondary endpoint)	..	..	0·0045†
n (%)	11 (21)	24 (45)	..
Within 24 h (exploratory endpoint)	..	..	0·058†
n (%)	16 (30)	26 (49)	..
Time to use of conventional attack treatment or worsened attack by 1 level or more on the PGI-S, h			
Within 12 h (secondary endpoint)	..	..	<0·0001*
Quartile 1	>12 (5·9 to >12)	3·0 (2·0 to 6·0)	..
Median	>12 (>12 to >12)	>12 (6·0 to >12)	..
Quartile 3	>12 (>12 to >12)	>12 (>12 to >12)	..
Within 24 h (exploratory endpoint)	..	..	0·0001*
Quartile 1	15·3 (5·9 to >24)	3·0 (2·0 to 6·0)	..
Median	>24 (>24 to >24)	>24 (6·0 to >24)	..
Quartile 3	>24 (>24 to >24)	>24 (>24 to >24)	..
Time to ≥50% reduction in composite VAS score for three consecutive timepoints, h			
Within 12 h (secondary endpoint)	..	..	<0·0001*
Quartile 1	2·5 (1·5 to 3·5)	6·0 (3·0 to >12)	..
Median	6·0 (3·0 to 9·0)	>12 (>12 to >12)	..
Quartile 3	>12 (9·0 to >12)	>12 (>12 to >12)	..
Within 24 h (exploratory endpoint)	..	..	<0·0001*
Quartile 1	2·5 (1·5 to 3·5)	6·0 (3·0 to 19·0)	..
Median	6·0 (3·0 to 9·0)	19·0 (19·0 to >24)	..
Quartile 3	18·0 (9·0 to >24)	>24 (>24 to >24)	..

Data in parentheses are 95% CIs or percentages. All assessment timepoints are measured from the time of study drug administration. n=number of attacks. PGI-C=Patient Global Impression of Change. PGI-S=Patient Global Impression of Severity. VAS=visual analogue scale. *Calculated using Gehan's generalised Wilcoxon test. †Calculated using Prescott's test.

Table 2: **Primary, secondary, and select exploratory outcomes assessed during part 2**

placebo; Gehan's generalised Wilcoxon test, p=0·0005; table 2). At 12 h and 24 h, fewer attacks treated with sebetralstat (eight [15%] of 53 attacks at 12 h and 11 [21%] of 53 attacks at 24 h) than those treated with placebo (16 [30%] of 53 at 12 h and 21 [40%] of 53 at 24 h) subsequently used conventional attack treatment, although at 12 h this difference was non-significant (p=0·060 for 12 h and p=0·034 for 24 h; figure 3A; appendix p 16).

Median time to symptom relief defined as the hereditary angioedema attack being rated at least "a little better" on the PGI-C scale for two consecutive timepoints was 1·6 h (95% CI 1·5–3·0) with sebetralstat versus 9·0 h (4·0–17·2) with placebo (p<0·0001; table 2). At 12 and 24 h after study drug administration, more attacks treated with sebetralstat were rated at least "a little better" for two consecutive timepoints (44 [83%] at 12 h and 45 [85%] at 24 h) compared with attacks treated with placebo (27 [51%] at 12 h and 34 [64%] at 24 h; p=0·0018 at 12 h and p=0·031 at 24 h; figure 3B).

Median time to an attack rated at least "better" on the PGI-C scale within 12 h and 24 h was significantly shorter for attacks treated with sebetralstat versus placebo (12 h: 5·0 [95% CI 2·1 to >12] *vs* >12 h [9·0 to >12], p=0·0003; at 24 h: 5·0 h [2·1 to 15·0] and 15·0 h [9·0 to 23·5]; p=0·0036; appendix p 14).

Median time to an attack rated at least "a little worse" on the PGI-C scale within 12 h and 24 h was significantly longer for attacks treated with sebetralstat versus placebo.

The median time to symptom relief, defined as an at least 50% reduction from baseline in the composite of the VAS measurements for three consecutive timepoints, was 6·0 h (95% CI 3·0–9·0) after sebetralstat treatment and was not calculable for the placebo group because fewer than 50% of attacks resulted in the endpoint (p<0·0001; table 2; figure 3C). At 12 and 24 h after study drug administration, more attacks treated with sebetralstat (33 [62%] at 12 h and 39 [74%] at 24 h) had symptom relief according to the composite VAS than attacks treated with placebo (16 [30%] at 12 h and 20 [38%] at 24 h; p=0·0014 for 12 h and p=0·0006 for 24 h; figure 3C). The estimates for composite VAS and index VAS were similar (table 2; appendix p 17).

Time to conventional attack treatment use or worsening in severity by 1 level or more on the PGI-S, whichever came first, within 12 h of study administration was significantly longer after treatment with sebetralstat than after treatment with placebo (p<0·0001; figure 3D). Median time to worsening within 12 h after sebetralstat treatment or placebo was not calculable, because fewer than 50% of attacks reached this endpoint.

A significantly lower proportion of attacks had worsened in severity by 1 level or more on the PGI-S or were associated with conventional attack treatment within 12 h after treatment with sebetralstat than after treatment with placebo (11 [21%] *vs* 24 [45%]; p=0·0045); there was no between-group difference at 24 h (16 [30%] *vs* 26 [49%]; p=0·58; figure 3D).

The median time to attack resolution, defined as a PGI-S rating of "none" within 24 h after study drug administration, was significantly shorter with sebetralstat than with

placebo (18·0 h [95% CI 10·0 to >24] *vs* >24 h [15·0 to >24] p=0·0021). A significantly higher proportion of attacks had complete attack resolution on the PGI-S within 24 h with sebetralstat than with placebo (28 [53%] of 53 *vs* 14 [26%] of 53; p=0·012); however, no difference was seen at 12 h (20 [38%] *vs* ten [19%]; p=0·062; appendix p 14).

The cumulative effect of sebetralstat on hereditary angioedema attack severity and symptoms expressed as AUCs showed significantly greater reductions from baseline with sebetralstat versus placebo for PGI-C, composite VAS, and PGI-S scores over 12 h from study drug administration (appendix pp 12, 18). A full list of

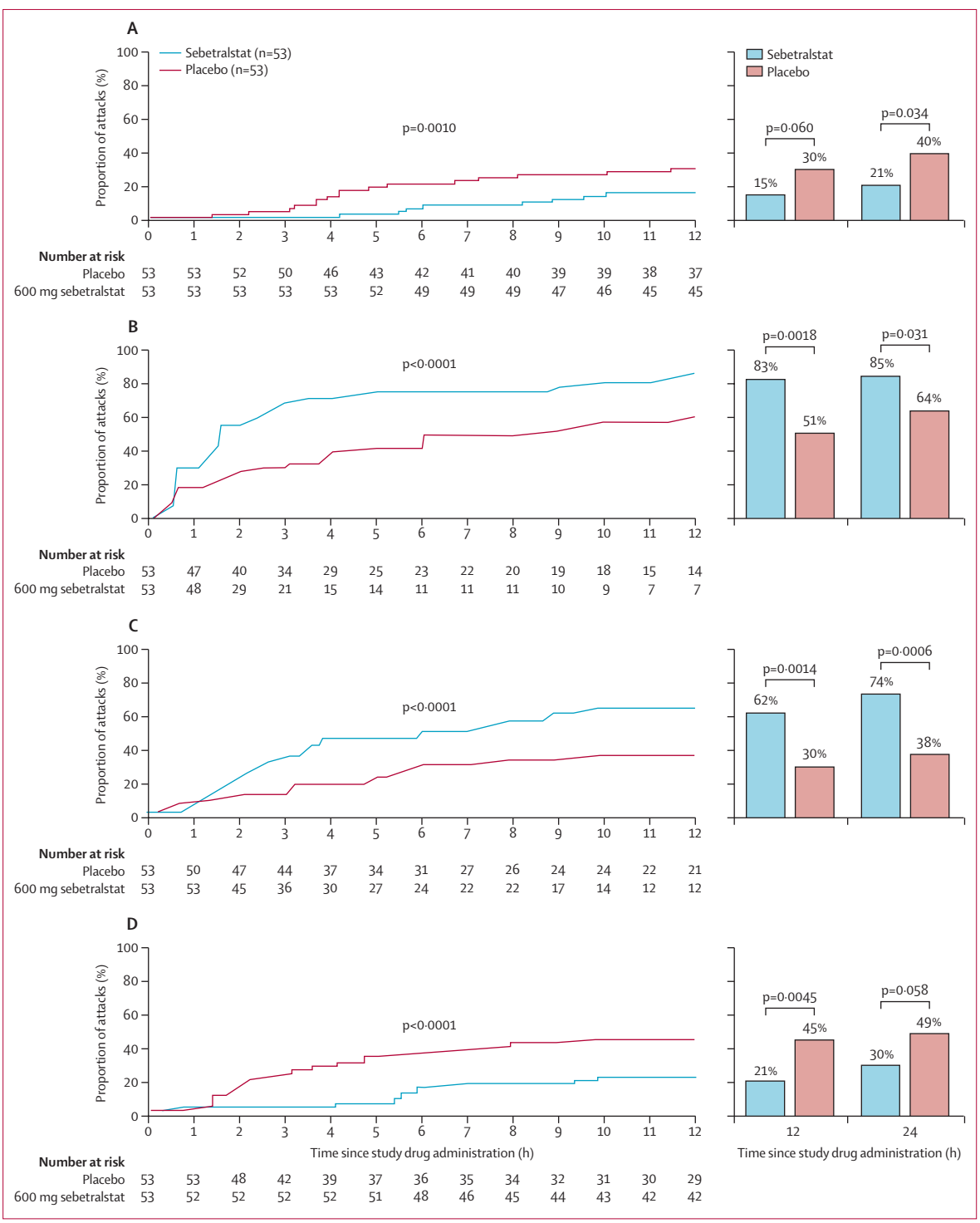

Figure 3: **Primary, secondary and select exploratory endpoints**
(A) Time to, and proportion of attacks, with the use of conventional attack treatment, within 12 h of study drug administration. (B) Time to symptom relief, and proportion of attacks, rated at least "a little better" on the PGI-C for two consecutive timepoints within 12 h of study drug administration. (C) Time to symptom relief, and proportion of attacks, rated using the VAS (defined as a 50% reduction from baseline in composite VAS measurements for three consecutive timepoints) within 12 h of study drug administration. (D) Time to, and proportion of attacks, with use of conventional attack treatment or worsening (≥1 level) from baseline on the PGI-S within 12 h of study drug administration.
53 participants included in the analyses were the participants who treated two hereditary angioedema attacks during part 2 of the study. p values for time-to-event data were determined using Gehan's generalised Wilcoxon test. p values for proportions between treatment arms were determined using Prescott's test. PGI-C=Patient Global Impression of Change. PGI-S=Patient Global Impression of Severity. VAS=visual analogue scale.

outcomes for exploratory endpoints is provided in the appendix (p 14). The carryover of the effects of the period and the treatment period interactions were assessed by the regression model analysis and were not statistically significant (data not shown).

No serious or life-threatening adverse events, deaths, or treatment discontinuations due to adverse events occurred. Overall, 25 (37%) of 68 partcipants had at least one treatment-emergent adverse event. Five (7%) of 68 participants had any drug-related treatment-emergent adverse event, and in part 2, three (5%) of 58 participants had any drug-related treatment-emergent adverse events while taking sebetralstat and two (4%) of 55 did while taking placebo (table 3). 14 (21%) participants had on-treatment treatment-emergent adverse events (ie, occurred within 48 h after study drug administration). Overall, on-treatment events were seen in fewer than 5% of participants, with the exception of headache (six events experienced by four [6%] of 68 participants; three with sebetralstat and one with placebo). No instances of vomiting occurred within 48 h of study drug administration during part 1 of the trial, and only two participants had on-treatment vomiting during part 2 of the trial (one event in one [2%] of 58 participants treated with sebetralstat, and two events in one [2%] of 55 participants treated with placebo; all attacks were peripheral at onset). A table summarising on-treatment adverse events is provided in the appendix (p 19). All instances of vomiting occurred more than 24 h after administration of the study drug, were deemed unrelated to the study drug, and resolved without further treatment (for vomiting). No serious on-treatment treatment-emergent adverse events occurred after treatment with sebetralstat or placebo. Most study drug-related on-treatment treatment-emergent adverse events were experienced by only one participant each, with the exception of headache (four events experienced by two [3%] participants) and flushing (two events experienced by two [3%] participants) during part 1 of the study. There were two drug-related treatment-emergent adverse events associated with sebetralstat treatment in the gastrointestinal system in this study: one event of nausea during part 1 and one event of abdominal pain during part 2. No clinically significant findings were noted with vital signs, physical exams, and ECGs.

	Part 1 (sebetralstat; N=68)	Part 2		Parts 1 and 2 combined	
		Sebetralstat (n=58)	Placebo (n=55)	Sebetralstat only (n=68)	Overall (N=68)
Any treatment-emergent adverse event	12 (18%)	14 (24%)	7 (13%)	22 (32%)	25 (37%)
Any on-treatment treatment-emergent adverse event*	7 (10%)	8 (14%)	5 (9%)	12 (18%)	14 (21%)
Severe treatment-emergent adverse events	1 (1%)	0	0	1 (1%)	1 (1%)
Any drug-related treatment-emergent adverse event	5 (7%)	3 (5%)	2 (4%)	6 (9%)	7 (10%)
Gastrointestinal disorders	1 (1%)	1 (2%)	1 (2%)	2 (3%)	3 (4%)
Abdominal pain	0	1 (2%)	0	1 (1%)	1 (1%)
Anal incontinence	0	0	1 (2%)	0	1 (1%)
Nausea	1 (1%)	0	0	1 (1%)	1 (1%)
Malaise	1 (1%)	0	0	1 (1%)	1 (1%)
Back pain	1 (1%)	1 (2%)	0	1 (1%)	1 (1%)
Nervous system disorders	3 (4%)	1 (2%)	1 (2%)	3 (4%)	3 (4%)
Dizziness	1 (1%)	0	0	1 (1%)	1 (1%)
Headache	2 (3%)	1 (2%)	1 (2%)	2 (3%)	2 (3%)
Flushing	2 (3%)	0	0	2 (3%)	2 (3%)

The most frequently occurring drug-related treatment-emergent adverse events in the safety set are shown. An adverse event was classified as treatment-emergent if it started or worsened on or after the time of study drug dosing. An adverse event was classified as severe if the event was intolerable, necessitated additional therapy or alteration of therapy, and interfered with the participant's daily activities. On-treatment was defined as occurring within 48 h post-dose. Drug-related treatment-emergent adverse events were defined as having a relationship to the study drug classified by the investigator as "suspected" or missing; "suspected" means that a reasonable possibility exists that the study drug caused the adverse event. *Occurring within 48 h after study drug administration.

Table 3: **Adverse events observed during part 1, part 2, and parts 1 and 2 of the study combined**

Discussion

In this phase 2 trial, on-demand treatment of hereditary angioedema attacks with a single 600 mg oral dose of sebetralstat significantly increased the time to use of conventional attack treatment versus placebo, meeting the primary endpoint. Additionally, through use of multiple patient-reported assessment methods, sebetralstat delivered faster symptom relief, reduced attack severity, and resulted in a faster time to attack resolution than placebo.[26,27]

Hereditary angioedema treatment guidelines recommend that attacks be treated as early as possible.[28–30] Previous trials have shown that early treatment results in a considerably shorter time to onset of symptom relief than delayed treatment initiation does.[31–33] Furthermore, treatment initiation within 1 h of attack onset significantly shortens time to resolution and overall duration of the attack.[32]

Although currently available on-demand therapies were initially studied and approved for health-care professional administration, all except ecallantide[18] are now indicated for self-administration.[34] Despite this transition, administration delays remain common. In observational trials, the median time from attack onset to self-administration for intravenous C1 inhibitor was 2 h,[35] and the median time from attack onset to self-administration with subcutaneous icatibant was similar at 1·5 h, with 25% of treatments delayed for 5 h or longer.[34] Potential reasons for treatment delays include inadequate patient training, time required for medication preparation in the setting of an attack, finding a discreet setting for administration of an injection or infusion, and hesitancy related to potential local injection-site reactions and pain.[36–39] Understandably, individuals with hereditary angioedema have cited route of administration as the most important factor in determining treatment

preference and expressed a desire to avoid injections in the US Food and Drug Administration's Patient-Focused Drug Development Initiative "The Voice of the Patient".[37] This finding was consistent with a mail-based survey conducted among individuals with laboratory-confirmed hereditary angioedema, which found that 76% of those who responded preferred a less-invasive route of administration than intravenous routes.[40]

By contrast with the delays observed with on-demand parenteral therapies,[30] almost all attacks in the current phase 2 trial (109 [96%] of 113) were treated within 1 h of onset, with a median time of 30 min from recognition of attack to administration of treatment, including the time required to verify attack eligibility with the trial physician before dosing. By reducing treatment burden, sebetralstat has the potential to decrease time to treatment administration, thereby improving clinical outcomes. An oral medication might lead to an increase in on-demand use of treatment; however, given the unpredictable nature of hereditary angioedema attacks, including potential for rapid progression, we believe the benefits would outweigh any potential risks.

In addition to early administration, the rapid response to sebetralstat reported by participants here might be attributed to its fast absorption and high plasma concentration after oral administration. Sebetralstat concentrations were approximately an order of magnitude above its half maximal inhibitory concentration in whole plasma (IC_{50} 54 nM [23·4 ng/mL])[24] within 15 min of administration, and plasma concentrations reached a maximum at 1·00 h. In part 1 of the trial, sebetralstat provided near-complete protection of plasma from prekallikrein activation and cleavage of high-molecular-weight kininogen beginning at 15 min and up to 4 h after drug administration, which was the last timepoint assessed. We acknowledge that the analysis of a representative subset of samples rather than the entire cohort is a limitation of the study; however, these data are consistent with previous phase 1 results.[23] Taken together, these data support a favourable pharmacokinetic and pharmacodynamic profile characterised by rapid absorption, high plasma concentration, and near-complete inhibition of plasma kallikrein within 30 min of administration. In the phase 1 trial, sebetralstat was also shown to protect against kininogen cleavage and suppress both plasma prekallikrein and factor XII activation, resulting in inhibition of the positive feedback loop responsible for the activation and propagation of the contact system. Inhibition of generation of plasma kallikrein after administration of sebetralstat might have contributed to the halting of attack progression seen in this trial.[24]

One potential obstacle for an oral drug in the context of acute treatment of hereditary angioedema attacks might be abdominal involvement, including symptoms of distension, cramping, nausea, and, less often, vomiting and diarrhoea. A recent literature review of articles published over the past decade (2010–20) indicated that gastrointestinal symptoms occurred in 43–93% of individuals with hereditary angioedema.[41] An earlier cross-sectional study found that, among 164 patients who had an attack in the past 6 months, the most common body site affected was the abdomen (32%) although 24% of individuals reported attacks in multiple locations, so this proportion might have been higher.[42] In the on-demand clinical trial setting, 154 (52%) of 296 hereditary angioedema attacks treated with ecallantide in the EDEMA studies involved abdominal symptoms;[43] similar proportions were reported in the FAST-3 controlled and open-label studies of icatibant (35–46%).[44] In the current study, 30 (27%) of 113 treated hereditary angioedema attacks included abdominal symptoms, which might under-represent the prevalence of abdominal involvement in hereditary angioedema attacks. Although no participants in our study had abdominal symptoms that precluded oral administration, this potential challenge must be assessed in a larger number of abdominal attacks to determine whether it represents an actual limitation of this treatment route.

Sebetralstat was well tolerated, and no serious adverse events were reported. Although the proportion of drug-related treatment-emergent adverse events was similar in attacks treated with sebetralstat and placebo, further trials investigating the safety profile of sebetralstat are warranted. Of note, two gastrointestinal adverse events occurred that were considered to be related to sebetralstat treatment. Although uncommon, these reports may take on added significance in the setting of hereditary angioedema, where attacks involving the abdomen are common. The preliminary safety profile noted in this trial contrasts meaningfully with the labelled adverse reactions for approved on-demand parenteral therapies, which include hypersensitivity, anaphylaxis, flushing, and urticaria, as well as several types of injection-site reactions including pain, redness, bruising, burning, erythema, pruritus, and swelling.[18–21] For one of the most commonly used subcutaneous on-demand treatments, icatibant, injection-site reactions occurred in 97% (75 of 77) of trial participants given icatibant compared with 33% (25 of 75) who were given placebo.[21]

The conditions set forth by the trial design imposed some additional limitations, including within-participant dependence of endpoints because the same participant crossed over between active treatment and placebo, and that relatively fewer frequent measurements were captured within the 12 h time frame, especially after 4 h, which might have led to delayed capture of participant-reported outcomes. Other limitations of this trial will be addressed in the ongoing phase 3 trial (NCT05259917), including the testing of two dose strengths (300 mg and 600 mg) versus placebo in a three-way crossover trial, participants' ability to use a second dose of study drug as part of the treatment regimen for an attack, the elimination of the requirement for study participants to interact with

their physicians to confirm eligibility of an hereditary angioedema attack, and the inclusion of nearly all hereditary angioedema attacks in all anatomical locations and breakthrough attacks in participants using prophylactic treatment.

In summary, sebetralstat is a novel, investigational, oral, on-demand treatment for hereditary angioedema attacks that provides a patient-preferred route of administration, potentially facilitating the early treatment of attacks by reducing treatment burden; rapid absorption and inhibition of plasma kallikrein activity and generation; early symptom relief and attack resolution; and a favourable preliminary safety profile in the context of approved parenteral therapies. Based on these results, a confirmatory phase 3 clinical trial for sebetralstat for the on-demand treatment of hereditary angioedema attacks is currently underway (NCT05259917).

Contributors

EA-P acted as the coordinating investigator and reviewed and approved the study report. EA-P, PKA, MDS, CMY, AM, and EPF accessed and verified the underlying study data. The first draft of the manuscript was written by EA-P, AZ, PKA, AM, and MMau. All authors reviewed and provided comments on subsequent drafts, had access to study data, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

EA-P has received grants from or has served as consultant or speaker for BioCryst, Biomarin, Centogene, CSL Behring, KalVista, Pharming, Pharvaris, and Shire/Takeda. AZ has received speaker or consultancy fees from BioCryst, CSL Behring, Pharming, and Takeda. DMC has received speaker fees or consultancy fees from BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharming, Pharvaris, and Shire/Takeda. MC has received funding for research projects from or served on advisory boards for CSL Behring, BioCryst, and Shire/Takeda. RH has received consultancy or speaker honoraria from CSL Behring, Shire/Takeda, and has served as a principal investigator for clinical trials sponsored by BioCryst, Pharvaris Netherlands BV, Pharming, CSL Behring, and KalVista. TK has received research grants from Takeda and speaker or consultancy fees from BioCryst, CSL Behring, KalVista and Takeda. MMag has been a speaker or advisor for or has received research funding from BioCryst, CSL Behring, KalVista, Octapharma, Pharming, and Shire/Takeda. IM-S has received speaker or consultancy fees from BioCryst, CSL Behring, Pharming, and Takeda. MS has received speaker and consultant fees from CSL Behring, Takeda, Pharming, and BioCryst. HF has received research grants from CSL Behring, Shire/Takeda, and Pharming and served as an advisor for BioCryst, KalVista, and ONO Pharmaceuticals. SK-A has received speaker or consultancy fees from BioCryst, CSL Behring, Pharming, and Takeda. VG-P has served as principal investigator for CSL Behring, Pharming, BioCryst, and KalVista. JAB has received speaker or consultancy fees from or served as principal investigator for KalVista, Celldex, Pharvaris, Biomarin, Amgen, Allakos, CSL Behring, Shire, Pharming, BioCryst, AstraZeneca, Sanofi-Regeneron, Novartis, and Genentech. HHL has received speaker or consultant fees from BioCryst, CSL Behring, Pharming, and Takeda. HJL has served as consultant, speaker, or engaged in research with or educational projects with BioCryst, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, and Takeda. PKA, MDS, CMY, DKL, and EPF are employees of KalVista Pharmaceuticals. AM was an employee of KalVista Pharmaceuticals at the time of the study. RG has received research grants from Takeda, BioCryst, KalVista, and Pharvaris and consulting and speaker fees from BioCryst, Fresenius Kabi, and Takeda. WRL is a member of advisory boards for BioCryst, CSL Behring, and Takeda; has received research grants from BioCryst, CSL Behring, Ionis, and Takeda; consulting fees from BioCryst, CSL Behring, Fresenius Kabi, Pharming, and Takeda; payments for lectures from CSL Behring, Pharming, and Takeda; and is an advisory board member of the US Hereditary Angioedema Association. AB has received research grants from Takeda and BioCryst and consulting fees from Takeda, BioCryst, Pharming, CSL, Pharvaris, KalVista, and Biomarin. MAR has received research grants from BioCryst, CSL Behring, Ionis, KalVista, Pharvaris; consulted for BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Ionis, KalVista, Pfizer, Pharming, Pharvaris, RegenexBio, Regeneron, Shire/Takeda, and Spark; and provided speaker presentations for CSL Behring, Grifols, Pharming, and Shire. MMau has been a speaker or advisor for or has received research funding from Alnylam, BioCryst, Centogene, CSL Behring, Dyax, KalVista, Pharming, Pharvaris, and Shire/Takeda.

Data sharing

Deidentified individual participant data that underlie the results reported in this Article will be shared within 6 months of sebetralstat approval in the EU or USA (whichever comes first) to qualified scientific and medical researchers. Proposals and data access requests can be submitted to medinfo@kalvista.com.

Acknowledgments

Scientific editorial review was provided by Zara Melyan, KalVista Pharmaceuticals. Medical writing assistance was provided under the direction of the authors by Reem Berro and Brittany Eldridge and editorial review was provided by Sandi Lusk and Laura Tendler, of Cadent Medical Communications, a Syneos Health group company, and was supported by KalVista Pharmaceuticals. AM was affiliated with KalVista Pharmaceuticals at the time of the study but is currently at the Institute of Health Policy, Management & Evaluation, University of Toronto, ON, Canada. Some of the results of this study were presented at the C1-Inhibitor Deficiency & Angioedema Workshop; 3–6 June 2021, Budapest, Hungary, and at the annual meeting of the European Academy for Allergy and Clinical Immunology; 10–12 July 2021, Madrid, Spain, and Krakow, Poland.

References

1 Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006; **119:** 267–74.

2 Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med* 2020; **382:** 1136–48.

3 Zanichelli A, Arcoleo F, Barca MP, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis* 2015; **10:** 11.

4 Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 2012; **109:** 395–402.

5 Lumry WR, Settipane RA. Hereditary angioedema: epidemiology and burden of disease. *Allergy Asthma Proc* 2020; **41** (suppl 1)**:** S08–13.

6 Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis* 2018; **13:** 73.

7 Joseph K, Tuscano TB, Kaplan AP. Studies of the mechanisms of bradykinin generation in hereditary angioedema plasma. *Ann Allergy Asthma Immunol* 2008; **101:** 279–86.

8 Konings J, Cugno M, Suffritti C, Ten Cate H, Cicardi M, Govers-Riemslag JW. Ongoing contact activation in patients with hereditary angioedema. *PLoS One* 2013; **8:** e74043.

9 Pixley RA, Schapira M, Colman RW. The regulation of human factor XIIa by plasma proteinase inhibitors. *J Biol Chem* 1985; **260:** 1723–29.

10 Schreiber AD, Kaplan AP, Austen KF. Inhibition by C1INH of Hagemann factor fragment activation of coagulation, fibrinolysis, and kinin generation. *J Clin Invest* 1973; **52:** 1402–09.

11 Kaplan AP, Pawaskar D, Chiao J. C1 inhibitor activity and angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol Pract* 2020; **8:** 892–900.

12 Kaplan AP, Joseph K. Pathogenesis of hereditary angioedema: the role of the bradykinin-forming cascade. *Immunol Allergy Clin North Am* 2017; **37:** 513–25.

13 Suffritti C, Zanichelli A, Maggioni L, Bonanni E, Cugno M, Cicardi M. High-molecular-weight kininogen cleavage correlates with disease states in the bradykinin-mediated angioedema due to hereditary C1-inhibitor deficiency. *Clin Exp Allergy* 2014; **44:** 1503–14.

14 Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 2001; **161:** 714–18.

15 Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010; **363:** 513–22.

16 Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010; **126:** 821–27.

17 Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010; **363:** 532–41.

18 Kalbitor [package insert]. Deerfield, IL: Takeda, 2009. https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed Dec 12, 2022).

19 Berinert [package insert]. King of Prussia, PA: CSL Behring, 2009. https://labeling.cslbehring.com/PI/US/Berinert/EN/Berinert-Prescribing-Information.pdf (accessed Dec 12, 2022).

20 Ruconest [package insert]. Leiden: Pharming, 2014. https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed Dec 12, 2022).

21 Firazyr [package insert]. Lexington, MA: Takeda Pharmaceuticals America, 2011. https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed Dec 12, 2022).

22 Chen M, Riedl MA. Emerging therapies in hereditary angioedema. *Immunol Allergy Clin North Am* 2017; **37:** 585–95.

23 Maetzel A, Smith MD, Duckworth EJ, et al. KVD900, an oral on-demand treatment for hereditary angioedema: phase 1 study results. *J Allergy Clin Immunol* 2022; **149:** 2034–42.

24 Duckworth EJ, Murugesan N, Li L, et al. Pharmacological suppression of the kallikrein kinin system with KVD900: an orally available plasma kallikrein inhibitor for the on-demand treatment of hereditary angioedema. *Clin Exp Allergy* 2022; **52:** 1059–70.

25 Feingold M, Gillespie BW. Cross-over trials with censored data. *Stat Med* 1996; **15:** 953–67.

26 Aygören-Pürsün E, Zanichelli A, Cohn DM, et al. A single on-demand treatment with orally administered KVD900 significantly slows progression and accelerates resolution of attacks in patients with hereditary angioedema (HAE): results of a phase 2, placebo-controlled, double-blind cross-over trial. *Allergy* 2021; **76** (Suppl 110)**:** 658–59.

27 Zanichelli A, Aygören-Pürsün E, Cohn DM, et al. Fast improvement of HAE attacks with the oral on-demand plasma kallikrein inhibitor KVD900: an analysis of the pharmacokinetic and pharmacodynamic profile of KVD900 and attack symptom severity during a double-blind, randomized phase 2 cross-over trial in patients with HAE type I and II. C1-Inhibitor Deficiency & Angioedema Workshop; June 3–6, 2021; Budapest, Hungary.

28 Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol* 2019; **15:** 72.

29 Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. *Allergy* 2018; **73:** 1575–96.

30 Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2021 revision and update. *Allergy* 2022; **77:** 1961–90.

31 Craig TJ, Rojavin MA, Machnig T, Keinecke HO, Bernstein JA. Effect of time to treatment on response to C1 esterase inhibitor concentrate for hereditary angioedema attacks. *Ann Allergy Asthma Immunol* 2013; **111:** 211–15.

32 Maurer M, Aberer W, Bouillet L, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PLoS One* 2013; **8:** e53773.

33 Maurer M, Aberer W, Caballero T, et al. The Icatibant Outcome Survey: 10 years of experience with icatibant for patients with hereditary angioedema. *Clin Exp Allergy* 2022; **52:** 1048–58.

34 Hernández Fernandez de Rojas D, Ibañez E, Longhurst H, et al. Treatment of HAE attacks in the Icatibant Outcome Survey: an analysis of icatibant self-administration versus administration by health care professionals. *Int Arch Allergy Immunol* 2015; **167:** 21–28.

35 Zanichelli A, Azin GM, Cristina F, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered C1 inhibitor (Berinert) in patients with hereditary angioedema: the SABHA study. *Orphanet J Rare Dis* 2018; **13:** 51.

36 Tuong LA, Olivieri K, Craig TJ. Barriers to self-administered therapy for hereditary angioedema. *Allergy Asthma Proc* 2014; **35:** 250–54.

37 US Food and Drug Administration, Center for Biologics Evaluation and Research. The voice of the patient. Hereditary angioedema. May, 2018. https://www.fda.gov/media/113509/download (accessed Dec 7, 2020).

38 Dempster J. Practicalities of a reduced volume formulation of a C1-INH concentrate for the treatment of hereditary angioedema: real-life experience. *Allergy Asthma Clin Immunol* 2018; **14:** 44.

39 Mühlberg H, Ettl N, Magerl M. An analysis of the teaching of intravenous self-administration in patients with hereditary angio-oedema. *Clin Exp Dermatol* 2016; **41:** 366–71.

40 Jose J, Lehman EB, Craig T. Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: implications for future therapies. *Allergy Asthma Proc* 2018; **39:** 74–80.

41 Staller K, Lembo A, Banerji A, Bernstein JA, Shah ED, Riedl MA. Consider hereditary angioedema in the differential diagnosis for unexplained recurring abdominal pain. *J Clin Gastroenterol* 2022; **56:** 740–47.

42 Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. *Allergy Asthma Proc* 2014; **35:** 47–53.

43 Rubinstein E, Stolz LE, Sheffer AL, Stevens C, Bousvaros A. Abdominal attacks and treatment in hereditary angioedema with C1-inhibitor deficiency. *BMC Gastroenterol* 2014; **14:** 71.

44 Lumry WR, Farkas H, Moldovan D, et al. Icatibant for multiple hereditary angioedema attacks across the controlled and open-label extension phases of FAST-3. *Int Arch Allergy Immunol* 2015; **168:** 44–55.