Oral deucrictibant for prophylaxis of hereditary angioedema attacks (CHAPTER-1): primary analysis of a randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Hereditary angioedema is a bradykinin-mediated, rare condition characterised by recurrent and potentially life-threatening attacks of subcutaneous and submucosal swelling. Bradykinin B2 receptor antagonism is a proven mechanism for on-demand treatment of attacks, but no evidence exists on its effects when used prophylactically. Deucrictibant is an investigational orally bioavailable bradykinin B2 receptor antagonist. We aimed to evaluate the efficacy, safety, and tolerability of two dose regimens of oral deucrictibant administered as prophylaxis against hereditary angioedema attacks.

Methods CHAPTER-1 was a multicentre, double-blind, placebo-controlled, randomised, phase 2 trial conducted in two parts, a double-blind placebo controlled first part and an open-label second part, with only part 1 reported here. Part 1 recruited adults (aged 18–75 years) with hereditary angioedema type 1 or 2 from 37 sites (university hospitals and accredited angioedema centres) across North America, Europe, and Israel. Patients required a documented history of three or more attacks within the last 3 consecutive months before screening or two or more during the screening period (up to 8 weeks) to be eligible. An interactive response technology system randomised eligible patients 1:1:1 to receive oral deucrictibant 20 mg daily, 40 mg daily, or matching placebo for 12 weeks. Randomisation to treatment groups was stratified by the baseline attack rate. Patients, investigators, site personnel, and the sponsor were blinded to treatment assignment. Masking was achieved with identically appearing deucrictibant and placebo capsules. The primary endpoint was the time-normalised number of investigator-confirmed attacks per 4 weeks (monthly attack rate) from weeks 1 to 12 and was assessed using the intention-to-treat set. The endpoint was analysed by comparing each deucrictibant group with the placebo group using a Poisson generalised linear model with a log link function and Pearson's χ^2 scaling of SEs to account for potential dispersion. The safety analysis set included all patients who were randomly assigned and who received one or more doses of study drug (deucrictibant or placebo). CHAPTER-1 is registered with ClinicalTrials.gov (NCT05047185) and is now complete.

Findings Between March 9, 2022, and June 19, 2023, 44 patients were screened. Of 34 patients who were randomly assigned, 11 patients received deucrictibant 20 mg, 12 patients received deucrictibant 40 mg, and 11 patients received the placebo, with a median follow-up of 85·0 days (IQR 84·0–86·0). 21 (62%) patients were female, 13 (38%) were male, and 34 (100%) patients were White. The least squares mean monthly attack rate (primary analysis) was 0·40 (95% CI 0·18–0·92) for deucrictibant 20 mg, 0·30 (0·11–0·81) for deucrictibant 40 mg, and 1·93 (1·30–2·88) for placebo; percent reduction in attack rate compared with placebo was 79·2% (95% CI 47·2–91·8) for deucrictibant 20 mg (p=0·0010) and 84·5% (95% CI 53·8–94·8) for deucrictibant 40 mg (p=0·0008). Treatment-related treatment-emergent adverse events were experienced by two (18%) patients receiving deucrictibant 20 mg, one (8%) patient receiving deucrictibant 40 mg, and one (9%) patient receiving the placebo; all were mild in severity (grade 1) and did not require dosing modification of the study drug. There were no serious adverse events or deaths in any treatment group.

Interpretation To the best of our knowledge, this trial provides the first clinical evidence and proof-of-concept for bradykinin B2 receptor antagonism as a therapeutic approach for the prevention of hereditary angioedema attacks and supports further investigation of oral deucrictibant for bradykinin-mediated angioedema.

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Introduction

Hereditary angioedema is a rare genetic condition manifesting as recurrent, unpredictable episodes of subcutaneous and submucosal swelling attacks.[1–3] Attacks are often painful, functionally disabling, and become life-threatening when involving the larynx.[1,3] Patients with

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Research in context

Evidence before this study

Despite advancements in the management of hereditary angioedema, a number of patients still experience inadequate response, tolerability issues and/or high treatment burden, with the majority of treatments administered as injections. Furthermore, although antagonism of the bradykinin B2 receptor has proven to be effective and well tolerated for on-demand treatment of attacks, to the best of our knowledge its prophylactic use has never been investigated before this trial. There remains an unmet need for additional prophylactic therapies combining ease of administration, injectable-like efficacy, and a well tolerated safety profile. We searched PubMed with the term "hereditary angioedema" in the title and filtered for articles published on randomised trials between March 1, 2020, and March 1, 2025, with no language restrictions. During this period, 20 articles were published, of which 16 focused on prophylactic therapies. Of these articles, six investigated the kallikrein inhibitors, berotralstat and lanadelumab; four investigated the prekallikrein-targeting antisense oligonucleotide, donidalorsen; three investigated plasma-derived C1-inhibitors; two investigated the human monoclonal antibody against activated factor XII (FXIIa), garadacimab; and one investigated in vivo CRISPR-based gene-editing targeting the gene encoding kallikrein B1 (KLKB1), NTLA-2002. Berotralstat, a kallikrein antagonist, was the only oral prophylactic therapy investigated in these articles. The remaining treatments investigated were administered parenterally, ie, subcutaneously or intravenously. No articles were found that investigated bradykinin B2 receptor antagonism for prophylaxis or that examined the same molecule in development for both prophylaxis and on-demand treatment of hereditary angioedema attacks.

Added value of this study

To the best of our knowledge, CHAPTER-1 is the first randomised, double-blind, placebo-controlled trial to evaluate bradykinin B2 receptor antagonism for prophylactic treatment of hereditary angioedema attacks. In this phase 2 trial, we found that orally administered deucrictibant significantly reduced the monthly attack rate compared with placebo and was associated with lower rates of moderate-to-severe attacks and of attacks treated with conventional on-demand therapy. Improvements in patient-reported health-related quality of life and disease control and higher levels of satisfaction were consistent with clinical findings. The safety profile of deucrictibant was similar to that of placebo. These efficacy and safety findings contribute to addressing the existing knowledge gap by providing the first proof-of-concept evidence on the effects of bradykinin B2 receptor antagonism for prophylaxis of hereditary angioedema attacks and support the continued investigation of oral deucrictibant in a phase 3 trial.

Implications of all the available evidence

Together with the findings from the RAPIDe-1 trial examining oral deucrictibant as an on-demand treatment of hereditary angioedema attacks conducted in parallel, outcomes of CHAPTER-1 provide the first clinical evidence, to the best of our knowledge, that antagonism of the bradykinin B2 receptor could be an effective and well tolerated approach when used prophylactically and that deucrictibant could be the first oral molecule for both the prevention and treatment of bradykinin-mediated angioedema attacks.

hereditary angioedema report enduring emotional and physical impairment, and reduced quality of life during as well as between attacks.[4–6]

In most types of hereditary angioedema, variants in genes encoding for regulators of the kallikrein-kinin system result in excess bradykinin formation, increased vascular permeability, and subsequent angioedema, causing swelling of extremities, face, gastrointestinal tract, and upper airways.[1–3] Activation of bradykinin B2 receptors on vascular endothelial cells initiates the oedematous reaction and, therefore, therapies for prophylaxis and treatment of angioedema attacks ultimately aim to prevent this step by inhibiting bradykinin synthesis or receptor binding.[7,8] Current prophylactic therapies, most of which are administered parenterally, target upstream reactions in the bradykinin-forming cascade and inhibit bradykinin synthesis.[7,9] Downstream antagonism of the bradykinin B2 receptor has proven to be efficacious for on-demand treatment of attacks,[10,11] but its prophylactic use has not been investigated before this trial.

Guidelines for hereditary angioedema management recommend long-term prophylactic treatment to achieve disease control and normalise health-related quality of life, while minimising treatment-associated burden.[3,12] The development of novel treatments for prophylaxis of angioedema attacks has focused on combining efficacy and safety comparable to existing injectable treatments together with easier and/or less frequent dosing.[9] Availability of oral therapies with these characteristics is an unmet need in hereditary angioedema management.[9,13,14]

Deucrictibant is a first-in-class, investigational, orally bioavailable, antagonist of the bradykinin B2 receptor under development for both long-term prophylaxis and on-demand treatment of hereditary angioedema attacks.[15,16] The aim of this study was to evaluate the efficacy, safety, and tolerability of two dose regimens of oral deucrictibant administered as prophylaxis against hereditary angioedema attacks. The results of part 1 of the phase 2 CHAPTER-1 trial represent to the best of our knowledge, the first clinical evidence of the effects of bradykinin B2 receptor antagonism as a therapeutic approach for the prevention of hereditary angioedema attacks.

Methods

Study design and participants

CHAPTER-1 was a phase 2 study that comprised the double-blind, placebo-controlled, randomised part 1 followed by the open-label extension part 2 (both the original and amended versions of the study protocol are provided in appendix pp 29–194 as well as the statistical analysis plan [appendix pp 202–236]). Part 1 was a 12-week evaluation of the efficacy and safety of two doses of deucrictibant, 20 mg daily and 40 mg daily; this portion is complete and results are reported herein. Patients completing part 1 could enrol into part 2, which was the open-label portion evaluating the long-term safety and efficacy of deucrictibant 40 mg. A global network of patient associations was engaged for recommendations of countries, potential sites, and investigators for the study. Patients were recruited from 37 sites, including university hospitals and accredited angioedema centres, across North America, Europe, and Israel (appendix pp 2–4). This trial was approved by institutional review boards or ethics committees (Frankfurt ethics committee reference number for the initial study approval: 2021-463-AMG Ethikkommission des Universitätsklinikums Frankfurt am Main) at study sites and conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice, and applicable local requirements. The full list of protocol amendments are provided in the appendix (pp 195–201); there were no protocol amendments or deviations from the protocol that affected the statistical analysis or quality of data. Eligible patients were adults (ie, those aged 18–75 years) with hereditary angioedema type 1 or 2 and a documented history of three or more attacks within the past 3 consecutive months before screening. If patients had fewer than three documented hereditary angioedema attacks in the 3 months before the screening visit, or were on prophylactic treatment, then they had to have had a minimum of two hereditary angioedema attacks during the screening period (up to 8 weeks). Eligible patients were not receiving other prophylactic angioedema treatments at screening. Patients who had previously discontinued long-term prophylaxis because of intolerance or a lack of efficacy could enter the study provided that they had not been exposed at least 2 weeks before screening for C1 inhibitor, berotralstat, attenuated androgens, or antifibrinolytics, and at least 11 weeks before screening for lanadelumab.

Other inclusion criteria were the requirement for patients to have reliable access and the ability to use standard-of-care treatments alone to effectively manage breakthrough hereditary angioedema attacks, patients having a bodyweight of 40 kg or more at screening, that patients were considered by the investigator as willing and able to adhere to all protocol requirements and capable of and compliant with data recording into an electronic Patient Reported Outcome tool, and that patients provided informed consent. As reproductive and development toxicity studies were not available for deucrictibant and potential effects of deucrictibant on the fetus were unknown, neither pregnant nor breast-feeding women were eligible. Females and male partners of females of childbearing potential were eligible if sexually abstinent or using medically acceptable contraception.

Biological sex (not gender; patients were given the choice of male or female for reporting sex) and race were sourced from patient-reported data captured in an electronic case report form. Patients were recruited by the study investigators and all patients provided written informed consent before enrolment. Patients with concomitant diagnoses of another form of chronic angioedema, abnormal hepatic or renal function, receiving angiotensin-converting enzyme inhibitors or strong CYP3A4 inhibitors or inducers were excluded from the study. The trial protocol outlines the complete eligibility criteria (appendix pp 59–61). The trial was registered with ClinicalTrials.gov (NCT05047185) and is now complete.

See Online for appendix

Randomisation and masking

An interactive response technology system (managed by Cenduit) generated the allocation sequence for patient randomisation. Using the interactive response technology system, site investigators then enrolled and randomised the patients to one of three groups with a ratio of 1:1:1 (appendix p 18): deucrictibant 20 mg daily, deucrictibant 40 mg daily, or placebo. Cenduit did not have any involvement in the trial beyond the interactive response technology system. Randomisation to treatment groups was stratified by the baseline attack rate before screening or confirmed during the screening period (1 to <2 attacks, 2 to <3 attacks, or ≥3 attacks per 4 weeks). Patients, investigators, site personnel, and the sponsor were blinded to treatment assignment. Patients were provided with a treatment wallet containing the study drug sealed in blisters. Masking was achieved with identically appearing deucrictibant and placebo capsules in identical wallets. The study drug labels were also blinded and contained a unique code. Treatment unblinding was permitted if deemed necessary by the investigator for the patient's medical safety.

Procedures

Patients enrolled in the study orally self-administered deucrictibant 20 mg daily (immediate-release capsule formulation 10 mg twice daily), deucrictibant 40 mg daily (20 mg twice daily), or placebo capsules. The study drug was taken after meals with 12 h (SD 2) between doses for 12 weeks. During the treatment period, follow-up visits occurred every 2 weeks starting at day 0 until day 56 and the final study visit was on day 84. Patients completed an end-of-study visit 4 weeks after the last dose of study drug, which could be waived if they continued to the open-label extension portion of the study. Patients could withdraw from the study at any time. An investigator

could remove a patient from the study if they became pregnant, showed substantial non-compliance with the study drug, had a clinical adverse event, laboratory abnormality, or other medical condition or situation that negatively affected the benefit–risk such that continued participation in the study would not be in the best interest of the patient, or if the patient met an exclusion criteria (previously unrecognised or newly developed) that precluded further study participation.

Demographic information and hereditary angioedema characteristics including year of diagnosis, family history, and type of hereditary angioedema were collected at screening for each patient. Patient baseline attack rates were obtained from medical records showing the number of attacks in the 3 months before screening or recorded during the 8-week screening period, which were computed as a monthly (per 4 weeks) baseline attack rate. Clinical laboratory tests, vital signs, physical examination, 12-lead electrocardiogram (ECG) were collected by the investigators at various timepoints throughout the treatment period. Females of childbearing potential also had serum pregnancy testing at screening and at pre-specified visits. Post-menopausal females had serum sampling to test for follicle-stimulating hormone at screening.

Patients used an electronic diary to record study drug administration and details of angioedema attacks, including any use of conventional on-demand therapy. Patients had to report attack details to trial sites within 72 h of the attack onset by entering details into the electronic Patient Reported Outcome tool. Investigators then assessed and confirmed the attacks with the patient during telephone contact or in-person if attack occurred within 72 h of a planned visit, and recorded details in an electronic case report form. Detailed guidance provided to the investigators for severity grading of hereditary angioedema attacks is outlined in the appendix (p 5). Patient-reported outcome assessments were also completed by the patients at various visits throughout the study to record health-related quality of life, disease control, and treatment satisfaction. Detailed tables of assessments and their timings are available in the protocol (appendix pp 107–108).

Adverse events were defined and assessed systematically according to the protocol and using the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). Clinically significant abnormalities were defined in the protocol as abnormalities that require investigation and/or treatment. Adverse events were reported through spontaneous reports by the patient, general questioning by the investigator, clinically significant abnormalities found during physical examination, or clinically significant findings from vital signs, ECG, or diagnostic test results including laboratory tests. The investigator was responsible for assessing adverse events, their severity using the Common Terminology Criteria for Adverse Events (appendix p 6), and their causal relationship to the study drug. An independent data monitoring committee reviewed safety data on a regular basis and ad hoc throughout the study.

Outcomes

The primary endpoint of part 1 was the number of investigator-confirmed hereditary angioedema attacks during the 12-week study period, expressed as the normalised number of attacks per month (4 weeks) or monthly attack rate. Secondary efficacy endpoints were the number of time-normalised investigator-confirmed moderate-to-severe attacks (severity grading described in the appendix p 5), the number of time-normalised investigator-confirmed attacks treated with on-demand medication during the 12-week study period, as well as the number of patients achieving a reduction in attack rate (ie, ≥50%, ≥70%, and ≥90%) relative to baseline, and the number of patients being attack-free at 12 weeks. Other secondary endpoints were the number and proportion of days with angioedema symptoms during the treatment period, the time to first investigator-confirmed hereditary angioedema attack in the treatment period, the number of investigator-confirmed hereditary angioedema attacks resulting in a visit to the emergency department or an admission to hospital during the treatment period, and pharmacokinetic parameters based on plasma concentration of deucrictibant and are intended to be reported elsewhere.

Safety endpoints were treatment-emergent adverse events, treatment-related treatment-emergent adverse events, and serious treatment-emergent adverse events. Clinical laboratory testing (haematology, biochemistry, coagulation, and urinalysis), vital signs, physical examination, and 12-lead ECG data were also assessed. Pre-specified exploratory patient-reported endpoints (instruments detailed in the appendix p 5), included the change in the total Angioedema Quality of Life (AE-QoL) questionnaire[17,18] score from baseline to week 12, the Patient Global Assessment of Change score at week 12, the 4-week Angioedema Control Test score,[19,20] and the 11-item Treatment Satisfaction Questionnaire for Medication (TSQM-II) score[21] at 12 weeks.

To standardise methodology and quality of assessments across countries and sites, clinical laboratory testing and 12-lead ECG data were assessed centrally, by Q² Solutions and IQVIA Connected Devices, respectively; all other safety, efficacy, and patient-reported outcome endpoints were assessed locally.

Statistical analysis

For the primary endpoint of time-normalised number of attacks, assuming a mean rate of 1·2 attacks per 4 weeks in placebo following a Poisson distribution, a sample size of 10 patients per group was expected to provide approximately 85% power to detect a treatment effect of 60% reduction in time-normalised number of attacks in each dose of deucrictibant compared with placebo at a

type I error rate of 5% for a two-sided test. Since this proof-of-concept phase 2 study was not designed to provide definitive confirmation of efficacy, as in a phase 3 study, a multiplicity correction for the two comparisons was not used. The primary endpoint and key secondary endpoints were analysed using the intention-to-treat analysis set (defined as all patients who were randomly assigned who received ≥1 dose of study drug) and also repeated using the per-protocol analysis set (all patients in the intention-to-treat analysis set without any major protocol deviations that could influence the validity of the data for the primary efficacy evaluations) as prespecified supplementary analyses.

For the primary efficacy endpoint, the monthly attack rate was calculated for each patient as the number of investigator-confirmed attacks occurring during the treatment period divided by the number of days the patient contributed to the treatment period multiplied by 28 days. The endpoint was analysed by comparing each deucrictibant group with the placebo group using a Poisson generalised linear model with a log link function and Pearson's χ^2 test scaling of SEs to account for potential dispersion. The model included fixed effects for treatment group (categorical), normalised baseline attack rate (continuous), and the randomised stratification factor of baseline attack rate (categorical, ≥1 and <2 or ≥2 attacks per month at baseline); an offset term, the logarithm of patient's follow-up time (in months) during the efficacy evaluation period, was incorporated to account for differences in time at risk. Early discontinuation was treated as an intercurrent event under a hypothetical strategy. Only attacks occurring while patients were under observation (ie, before discontinuation) were included in the model. Post-discontinuation outcomes were treated as missing data and assumed to be missing at random conditional on the observed history. Under this approach, no extrapolation of attack rates beyond each patient's observed follow-up time was required. The estimated least squares mean rate for each deucrictibant group and the mean rate ratios relative to the placebo group were provided with 95% CIs. These estimates were reported as monthly attack rates by transforming the estimates using the exponential function and scaling by the unit of time.

The treatment effect was tested using a Wald-based χ^2 test. A non-parametric approach using the Wilcoxon two-sample test was also performed. For sensitivity to the Poisson model assumption, a Negative Binomial regression model was also used. In a pre-specified analysis, percent reduction in attack rate was calculated as the difference in attack rate during the treatment period from baseline divided by the placebo attack rate and multiplied by 100. The analyses of the secondary efficacy endpoints were supportive; all statistical tests comparing treatments were descriptive in nature and were made without adjustment for multiplicity. The secondary efficacy endpoints were analysed using a Poisson regression model, if applicable, or descriptively as summary statistics including the number and proportion of patients with the event of interest. We also performed post-hoc analyses of percentage change from baseline in attack rates by month-interval and of monthly per treatment group by location (ie, abdominal, peripheral, or laryngeal). In a post-hoc analysis to evaluate the effects of using bradykinin B2 receptor antagonism for both prophylactic and on-demand treatment, we compared the mean attack duration in patients who used icatibant once as an on-demand treatment in the deucrictibant and placebo groups. Due to the low use of on-demand treatment in the deucrictibant groups during part 1, the set included hereditary angioedema attacks from both part 1 and the part 2 open label extension data cutoff (June 10, 2024) of the CHAPTER-1 study. Duration of attack was evaluated from the attack start and end, as recorded by patients in the electronic diary and is provided as mean (SD) for the deucrictibant and placebo groups.

Descriptive analyses were performed for pre-specified patient-reported outcomes with no adjustment for baseline differences between treatment groups or missing values at week 12.

Safety endpoints were analysed using the safety analysis set (defined as all patients randomly assigned who received ≥1 dose of study drug). The number and percentage of patients with treatment-emergent adverse events were tabulated by body System Organ Class and Preferred Term using the MedDRA (version 26.0) by treatment group. Comparisons are therefore descriptive. Serious treatment-emergent adverse events and treatment-emergent adverse events leading to discontinuation of study drug, study discontinuation, or death were summarised separately. Blood glucose concentrations and systolic and diastolic blood pressure at each visit is provided at the patient-level and mean group-level. The statistical analysis plan provides additional information (appendix pp 202–236). All analyses were performed using SAS (version 9.4 or higher).

Role of the funding source

The sponsor participated in the trial design and conduct, data collection, management, analysis, interpretation, and manuscript review. The sponsor also funded a medical writer to develop the initial manuscript draft.

Results

Between March 9, 2022, and June 19, 2023, 44 patients were screened, of which 34 were randomly assigned and received one or more doses of the study drug in part 1 (intention-to-treat analysis set and safety analysis set): 11 patients were assigned to deucrictibant 20 mg, 12 to deucrictibant 40 mg, and 11 placebo (figure 1; appendix p 18). Median follow-up for all 34 patients was 85·0 (IQR 84·0–86·0) days. Of the 10 patients who were

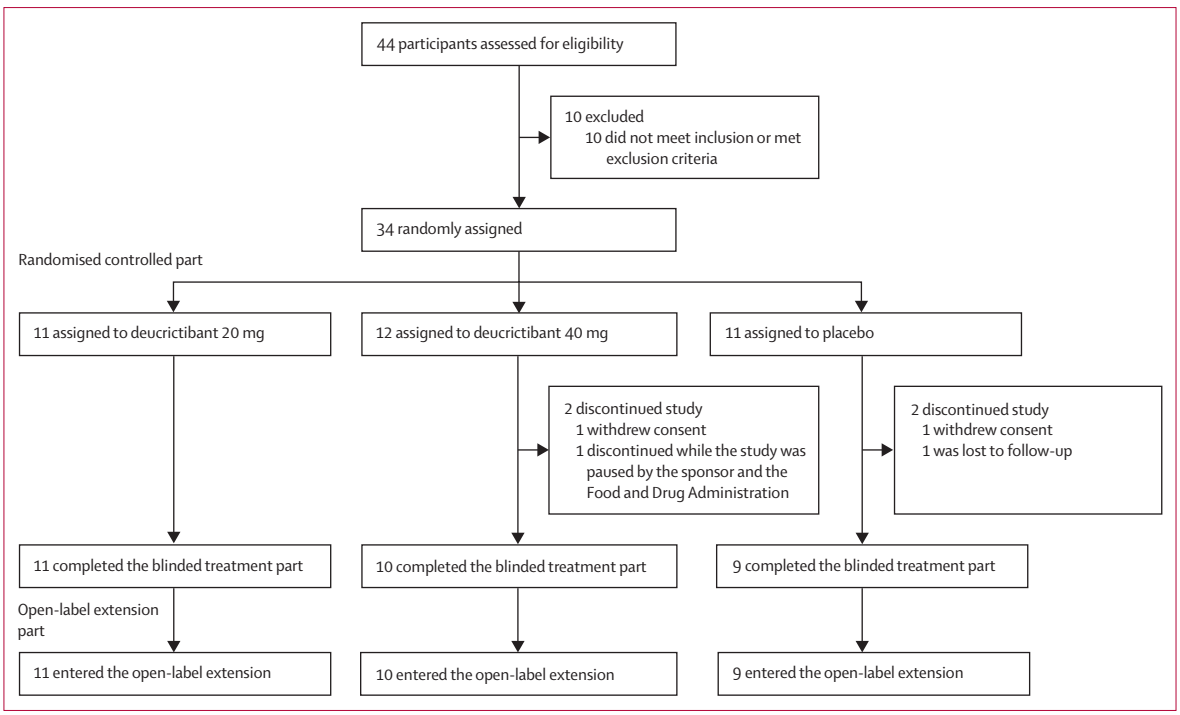

Figure 1: **Trial profile**

	Deucrictibant 20 mg group (n=11)	Deucrictibant 40 mg group (n=12)	Placebo group (n=11)
Age, years	36 (25–44)	39 (30–52)	40 (31–59)
Sex			
Male	6 (55%)	4 (33%)	3 (27%)
Female	5 (45%)	8 (67%)	8 (73%)
Race			
White	11 (100%)	12 (100%)	11 (100%)
BMI, kg/m^2	30 (24–32)	26 (23–28)	24 (22–28)
Hereditary angioedema type			
Type 1	9 (82%)	12 (100%)	10 (91%)
Type 2	2 (18%)	0	1 (9%)
Years since hereditary angioedema diagnosis	15 (6–22)	19 (8–28)	17 (8–22)
Baseline hereditary angioedema attack rate (attacks per month)†	1·67 (1·33–3·00)	1·74 (1·17–3·50)	1·67 (1·33–2·00)
Randomised baseline hereditary angioedema attack rate categories			
1 to <2 attacks per 4 weeks	7 (64%)	7 (58%)	6 (55%)
2 to <3 attacks per 4 weeks	1 (9%)	1 (8%)	2 (18%)
≥3 attacks per 4 weeks	3 (27%)	4 (33%)	3 (27%)
Patients with hereditary angioedema prophylaxis treatment use at any time before screening			
Berotralstat	1 (9%)	0	1 (9%)
C1 inhibitor, plasma derived	1 (9%)	0	0
Danazol	1 (9%)	1 (8%)	0

Data are n (%) or median (IQR) unless otherwise stated. *The safety analysis set included all randomly assigned patients who received ≥1 dose of the study drug (deucrictibant or placebo). †1 month equals 4 weeks.

Table 1: **Demographics and baseline clinical characteristics (safety analysis set)***

excluded during screening, all reasons were secondary to not meeting the study eligibility criteria. Reasons were due to C1-INH function of more than 50% (four patients), and hereditary angioedema medical history not meeting eligibility criteria (one patient), pregnancy or breastfeeding (one patient), concomitant diagnosis of other forms of angioedema (one patient), not meeting contraception requirements (one patient), baseline attack rate below requirement (one patient), and use of long-term prophylaxis within 2 weeks before screening (one patient).

Median age was 36 years (IQR 25–44) in the deucrictibant 20 mg group, 39 years (30–52) in the deucrictibant 40 mg group, and 40 years (31–59) in the placebo group (table 1). All 34 patients were White, 21 (62%) patients were female, and 13 (38%) were male. Female participants were five (45%) of 11 patients in the deucrictibant 20 mg group, eight (67%) of 12 in the deucrictibant 40 mg group, and eight (73%) of 11 patients in the placebo group. All 30 patients who completed part 1 enrolled in the part 2 long-term open-label extension.

The on-study least squares mean monthly attack rate was 0·40 (95% CI 0·18–0·92) for deucrictibant 20 mg group, 0·30 (0·11–0·81) for deucrictibant 40 mg group, and 1·93 (1·30–2·88) for placebo group (figures 2, 3; table 2). Percent reduction in attack rate compared with placebo was 79·2% (95% CI 47·2–91·8) for deucrictibant 20 mg (p=0·0010) and 84·5% (95% CI 53·8–94·8) for deucrictibant 40 mg (p=0·0008; table 2). In post-hoc analysis, the mean attack rate decreased at the first

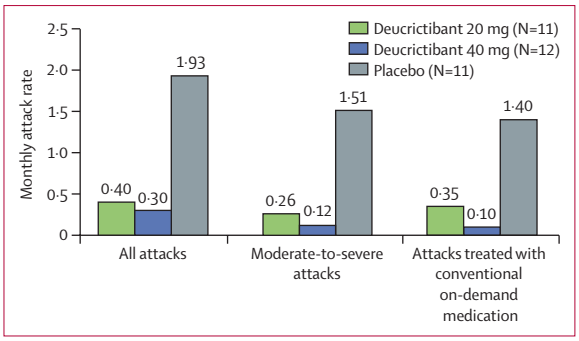

Figure 2: **Rate of hereditary angioedema attacks**
The least squares mean monthly attack rate. Monthly attack rate calculated as the number of investigator-confirmed attacks occurring during the treatment period divided by the number of days the patient contributed to the treatment period multiplied by 28 days.

assessment at week 1 and remained low thereafter through week 12 for both deucrictibant groups, whereas it remained steadily above baseline levels for placebo (appendix p 19). Consistent attack rate reductions in the deucrictibant groups compared with placebo were observed independent from baseline attack rates (appendix p 20). In post-hoc analyses, attack rate reductions in the deucrictibant groups were also consistently observed across abdominal, peripheral, and laryngeal locations (appendix p 7). Sensitivity and supplementary analyses also led to conclusions consistent with those of the primary statistical analyses, further supporting the robustness of the primary findings (appendix p 8). The only major protocol deviation was for a patient in the placebo group who was randomly assigned according to the incorrect stratification of baseline hereditary angioedema attack rate. In the prespecified analysis following the statistical analysis plan, this deviation did not influence the validity of the data for the primary efficacy evaluations.

Compared with placebo, the estimated reduction in rate of moderate-to-severe attacks through week 12 was 83·05% (95% CI 38·95–95·29) for the deucrictibant 20 mg group and 92·37% (50·90–98·81) for the deucrictibant 40 mg group (figures 2, 3; table 2). The estimated reduction in rate of attacks treated with conventional on-demand medication was 74·91% (95% CI 30·15–90·99) for the deucrictibant 20 mg group and 92·61% (56·78–98·74) for the deucrictibant 40 mg group (figures 2, 3; table 2). The majority of attacks using conventional on-demand medication were treated with the subcutaneously administered B2 receptor antagonist icatibant (36 [56%] of 64 attacks; appendix p 9). 25 attacks in the placebo group in part 1 (N=5) and 20 attacks in the deucrictibant groups across parts 1 and 2 (N=8) were treated once with the bradykinin B2 receptor antagonist icatibant as on-demand treatment (appendix p 10). In a post-hoc analysis, the mean attack duration was 1·12 (SD 1·06) and 1·05 (0·98) days in the placebo-icatibant and deucrictibant-icatibant groups, respectively (appendix p 10).

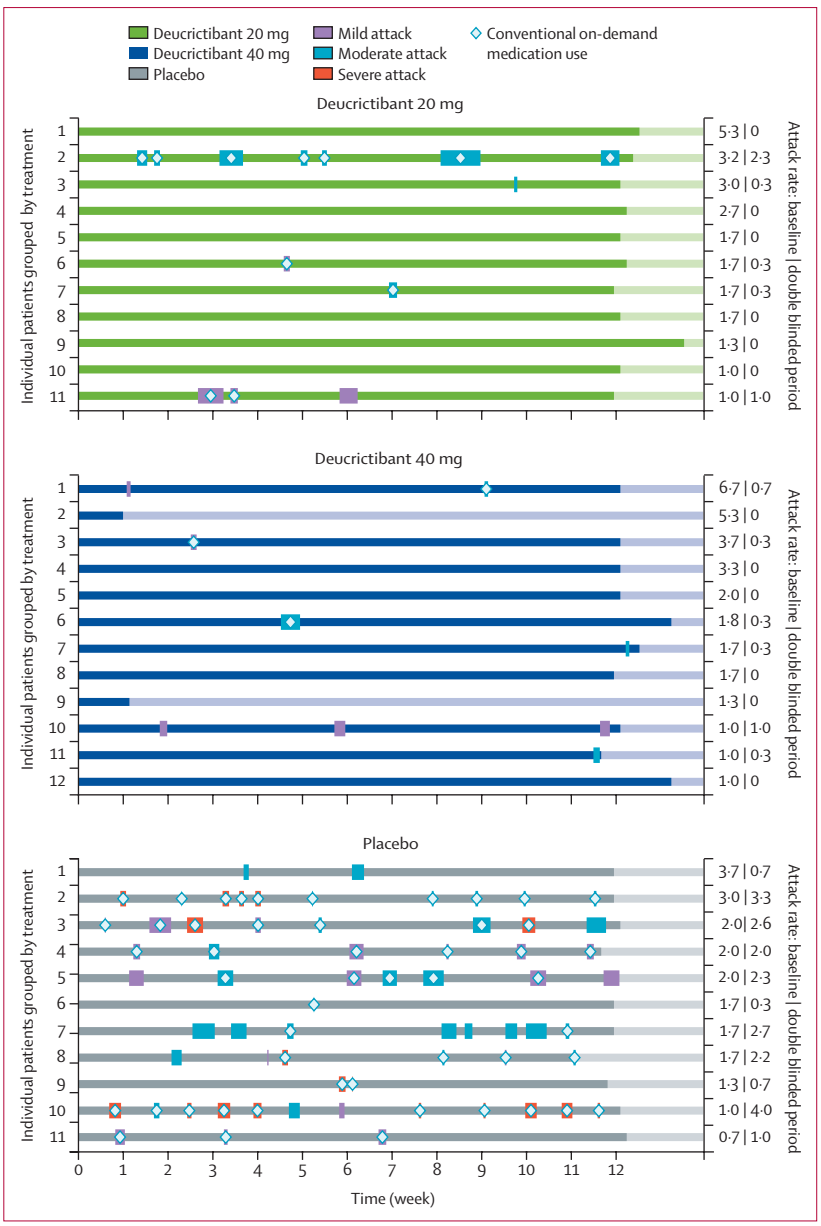

Figure 3: **Overview of hereditary angioedema attacks and the use of conventional on-demand medication**
The timepoint and severity of each attack experienced by individual patients in each treatment group are shown, as is any use of conventional on-demand treatment to manage attacks. The monthly attack rate at baseline and during the double-blinded period is also provided. Attacks are defined as mild, moderate, or severe based on the effect of symptoms on the patient's daily activities (appendix p 5).

A 50% or more, a 70% or more, and a 90% or more reduction in attack rate compared with baseline and an attack-free status were observed in a greater proportion of patients who received 4 weeks or more of deucrictibant than placebo (appendix p 21). Among patients receiving placebo, at week 12, 18% had a ≥50% reduction in attack rate and no patient was attack-free nor had a ≥90% reduction in attack rate.

Greater improvements in mean AE-QoL scores were observed at week 12 in the deucrictibant groups than in

	Deucrictibant 20 mg group (n=11)	Deucrictibant 40 mg group (n=12)	Placebo group (n=11)
Primary endpoint			
Overall rate of hereditary angioedema attacks, LSM (95% CI)†	0·40 (0·18–0·92)	0·30 (0·11–0·81)	1·93 (1·30–2·88)
Percent reduction *vs* placebo (95% CI)	79·24 (47·23–91·83)	84·46 (53·83–94·77)	..
Mean rate ratio *vs* placebo (95% CI)	0·21 (0·08–0·53)	0·16 (0·05–0·46)	..
p value	0·0010	0·0008	..
Secondary endpoints			
Rate of moderate-to-severe hereditary angioedema attacks, LSM (95% CI)	0·26 (0·08–0·81)	0·12 (0·02–0·67)	1·51 (0·91–2·52)
Percent reduction *vs* placebo (95% CI)	83·05 (38·95–95·29)	92·37 (50·90–98·81)	..
Mean rate ratio *vs* placebo (95% CI)	0·17 (0·05–0·61)	0·08 (0·01–0·49)	..
Rate of hereditary angioedema attacks treated with conventional on-demand medication, LSM (95% CI)	0·35 (0·14–0·85)	0·10 (0·02–0·56)	1·40 (0·88–2·24)
Percent reduction *vs* placebo (95% CI)	74·91 (30·15–90·99)	92·61 (56·78–98·74)	..
Mean rate ratio *vs* placebo (95% CI)	0·25 (0·09–0·70)	0·07 (0·01–0·43)	..
Patients who received ≥4 weeks of treatment with	(n=11)	(n=10)	(n=11)
≥50% reduction in attack rate relative to baseline	9 (82%)	9 (90%)	2 (18%)
≥70% reduction in attack rate relative to baseline	9 (82%)	8 (80%)	2 (18%)
≥90% reduction in attack rate relative to baseline	6 (55%)	6 (60%)	0
Attack-free status	6 (55%)	4 (40%)	0

LSM=least squares mean. *The intention-to-treat analysis set included all randomly assigned patients who received ≥1 dose of the study drug (deucrictibant) or placebo. †All attack rates shown are monthly (per 4 weeks).

Table 2: **Primary and key secondary efficacy endpoints (intention-to-treat analysis set)***

the placebo group, with the largest changes in the fear and shame and functioning domain scores (appendix pp 11–12, 22). Improvement in Patient Global Assessment of Change-measured health-related quality of life compared with baseline was also reported by higher proportions of patients who received deucrictibant than those who received placebo (appendix p 23). Mean angioedema control test scores at week 12 were 14·20 (SD 3·05; compared with 9·20 [4·61] at baseline) for the deucrictibant 20 mg group, 14·10 (2·47; 8·08 [3·09] at baseline) for the deucrictibant 40 mg group, and 8·38 (4·57; 7·09 [2·74] at baseline) for the placebo group; nine (90%) of ten patients who received deucrictibant (at either dose) had well controlled disease at week 12 compared with three (38%) of eight patients who received the placebo (appendix pp 13, 24). Patients who received deucrictibant reported higher treatment satisfaction than those who received placebo based on the Treatment Satisfaction Questionnaire for Medication (version 2) global score and effectiveness domain scores. Mean treatment satisfaction for the subdomain global score for those receiving deucrictibant 20 mg daily was 89·2 and for those receiving deucrictibant 40 mg daily was 85·8, compared with 59·4 for placebo. Additionally, mean treatment satisfaction for the subdomain effectiveness for those receiving deucrictibant 20 mg daily was 90·0 and for those receiving deucrictibant 40 mg daily was 86·7, compared with 50·0 for placebo. No evident differences in side-effects and convenience domain scores were observed between groups (appendix p 25). Treatment adherence in this study was evaluated from recoverability of treatment wallets at the study end with 31 (91%) of 34 patients having 90% or more adherence (appendix p 14).

Among 34 patients in the safety analysis set, 20 (59%) reported treatment-emergent adverse events, whose incidence and distribution were similar across groups (table 3; appendix pp 15–16). No severe or serious adverse events, no adverse events leading to study drug or study discontinuation, and no deaths were reported. No dosing modifications were required. Four patients each reported one treatment-related adverse event of mild severity: nausea and postural dizziness upon standing with deucrictibant 20 mg; increase in gamma-glutamyltransferase above normal levels with deucrictibant 40 mg; and headache with placebo. The event of increased gamma-glutamyltransferase that occurred in a single patient after 2 weeks of treatment remained mild in severity and less than 2 times the upper limit of normal throughout study part 1 and resolved while continuing treatment with deucrictibant 40 mg during the part 2 open-label extension; there were no other associated abnormalities in liver function tests or clinically evident manifestations observed. No other treatment-related changes in laboratory values, blood glucose concentrations (appendix p 26), or vital signs, including peripheral systolic and diastolic blood pressure (appendix p 27), were reported. All ECG intervals, including QT, remained stable without clinically relevant changes and with no abnormalities in morphology (appendix p 17). QRS intervals of more than 110 ms in two patients were deemed as non-clinically significant by the investigators (appendix p 17). The patient who had

elevated blood glucose levels at the time of screening was later diagnosed with type 2 diabetes, which was reported as unrelated to treatment by the investigator (appendix p 26).

Discussion

To the best of our knowledge, the results of the placebo-controlled part 1 of this phase 2 trial provide the first evidence of the clinical efficacy and safety of bradykinin B2 receptor antagonism for prophylaxis of hereditary angioedema attacks. Treatment with the orally administered bradykinin B2 receptor antagonist deucrictibant significantly reduced the occurrence of angioedema attacks per month, with a 79·2% reduction in mean attack rate for those receiving deucrictibant 20 mg daily and 84·5% for those receiving deucrictibant 40 mg daily compared with placebo. A reduction in the attack rate in the deucrictibant-treated groups was observed by week 1 and sustained through to the study end. Robustness of treatment effects was shown as deucrictibant reduced the attack rate compared with placebo irrespective of baseline attack rate and consistent treatment effects were observed across attack locations in post-hoc analyses.

Additional findings in this proof-of-concept study were supportive of the primary endpoint with reductions in the frequency and severity of attacks and the occurrence of attacks treated with conventional on-demand therapy. Icatibant was the most frequently used on-demand therapy, with a post-hoc analysis showing comparable onset-to-resolution attack durations for patients using icatibant as an on-demand therapy in the deucrictibant or placebo groups, suggesting no evident impairment of efficacy of on-demand treatment with a bradykinin B2 receptor antagonist when used for breakthrough attacks during exposure to a prophylactic treatment with the same mechanism of action. More favourable responses to deucrictibant compared with placebo were also observed in patient-reported health-related quality of life, disease control, and treatment satisfaction. Greater clinically meaningful changes (≥6 points)[18] in health-related quality of life as well as achievement of good disease control were also observed by week 4 of treatment with deucrictibant compared with placebo and sustained thereafter. Additionally, mean treatment satisfaction scores on the global and effectiveness domains were higher in patients who received deucrictibant compared with patients who received placebo. In a placebo-controlled phase 3 trial of subcutaneous plasma-derived C1 inhibitor 40 international units per kg and 60 international units per kg, mean treatment satisfaction score for this subdomain at week 14 was 86·83 and 80·72, respectively, compared with 45·22 (high-volume) and 50·60 (low-volume) for placebo.[22] Variations in size, duration, and design of clinical trials investigating drugs for prophylactic treatment of hereditary angioedema attacks prevent direct outcome comparisons.

	Deucrictibant 20 mg group (n=11)	Deucrictibant 40 mg group (n=12)	Placebo group (n=11)
Patients with at least 1 treatment-emergent adverse event	6 (55%)	7 (58%)	7 (64%)
Any treatment-related treatment-emergent adverse event	2 (18%)	1 (8%)	1 (9%)
Infections	3 (27%)	2 (17%)	2 (18%)
Nasopharyngitis	2 (18%)	0	1 (9%)
Urinary tract infection	1 (9%)	1 (8%)	0
Gastrointestinal infection	0	1 (8%)	1 (9%)
Viral pharyngitis	1 (9%)	0	0
Gastrointestinal disorders	2 (18%)	2 (17%)	4 (36%)
Diarrhoea	1 (9%)	1 (8%)	0
Abdominal pain	1 (9%)	0	1 (9%)
Nausea	1 (9%)	0	1 (9%)
Toothache	0	1 (8%)	0
Abdominal pain upper	0	0	2 (18%)
Constipation	0	0	1 (9%)
Dyspepsia	0	0	1 (9%)
Vomiting	0	0	1 (9%)
Investigations†	2 (18%)	2 (17%)	0
Gamma-glutamyltransferase increased	1 (9%)	1 (8%)	0
Blood alkaline phosphatase increased	1 (9%)	0	0
Blood glucose increased	1 (9%)	0	0
Protein urine present	0	1 (8%)	0
Reproductive system and breast disorders	1 (9%)	2 (17%)	1 (9%)
Dysmenorrhoea	0	1 (8%)	0
Genital haemorrhage	0	1 (8%)	0
Vaginal discharge	1 (9%)	0	0
Menstruation irregular	0	0	1 (9%)
General disorders and administration-site conditions	0	2 (17%)	0
Chest pain	0	1 (8%)	0
Feeling cold	0	1 (8%)	0
Injury, poisoning, and procedural complications	1 (9%)	1 (8%)	2 (18%)
Arthropod bite	0	1 (8%)	0
Ligament injury	1 (9%)	0	0
Ligament sprain	0	0	1 (9%)
Limb injury	0	0	1 (9%)
Musculoskeletal and connective tissue disorders	1 (9%)	0	1 (9%)
Muscle twitching	1 (9%)	0	0
Back pain	0	0	1 (9%)
Nervous system disorders	1 (9%)	0	1 (9%)
Dizziness postural	1 (9%)	0	0
Headache	0	0	1 (9%)
Respiratory, thoracic, and mediastinal disorders	0	1 (8%)	0
Cough	0	1 (8%)	0

Data are number of patients with event (%). Mild (grade 1) and moderate (grade 2) treatment-emergent adverse events are presented combined and no adverse events of grade 3 or worse occurred. If a patient experienced more than one treatment-emergent adverse event within a System Organ Class (or Preferred Term), the patient was counted once under that System Organ Class (or Preferred Term). *The safety analysis set included all randomly assigned patients who received one or more doses of the study drug (deucrictibant) or placebo. †Occurrences of values that were greater than the laboratory upper limit of normal.

Table 3: **All reported treatment-emergent adverse events (safety analysis set)***

In our trial, the mean monthly attack rate of about two attacks per month in the placebo group at baseline was similar to that of placebo groups in other prophylaxis trials;[23–26] it then remained stable during treatment through to the study end. At week 12, less than 20% of patients in the placebo group had a 50% or greater reduction in attack rate compared with their own baseline and none had a 90% or greater reduction. Some changes in patient-reported outcomes were observed in the placebo group, but these remained consistently more limited than those in the deucrictibant groups: the baseline-to-week-12 mean change in the AE-QoL score was higher than the minimally clinically important difference in the placebo group but was less than 50% of the change in the deucrictibant 40 mg group. About one-third of patients treated with placebo reported an improvement in their Patient Global Assessment of Change score compared with 90% of patients treated with deucrictibant 20 mg and 100% of patients treated with deucrictibant 40 mg. The mean angioedema control test score in the placebo group temporarily improved at week 8, but at week 12 about two thirds of the placebo group had poorly controlled disease compared with 90% reporting well controlled disease in the deucrictibant groups. Future trials of deucrictibant for prophylaxis will seek to confirm these observations on both objective clinical measures and subjective patient-reported outcomes.

The observed safety profile of deucrictibant was similar to placebo during 12 weeks of continued treatment. Three treatment-related events in the deucrictibant groups were mild in severity, manageable, and did not require changes in study drug administration. No events related to the effects of bradykinin B2 receptor antagonism on cardiovascular function, haemodynamic parameters, or glucose metabolism were observed. In phase 3 clinical trials of hereditary angioedema prophylactic treatments, the most common adverse events in the study-drug treated groups were gastrointestinal symptoms for oral berotralstat and, generally, injection-site reactions and/or headaches for parenterally administered treatments.[23–28] In the CHAPTER-1 study, one patient reported gastrointestinal symptoms unrelated to treatment and the oral administration inherently avoided injection-site reactions associated with parenteral administration. Patient-reported satisfaction with the study drug for side-effects did not differ between deucrictibant and placebo groups, indicating a comparable perceived tolerability. Another phase 2 trial of deucrictibant for on-demand treatment of hereditary angioedema attacks also showed that bradykinin B2 receptor antagonism was well tolerated, as already observed in trials investigating icatibant with the exception of injection-site reactions.[10,11] The continued daily use of deucrictibant for prophylaxis during the CHAPTER-1 trial showed no safety signals and a comparable safety profile to placebo. Larger and longer trials are warranted to further verify these safety results.

Achievement of disease control is the main goal of long-term prophylaxis in hereditary angioedema, ideally with minimal side-effects and treatment burden.[12] Despite the availability of effective treatments, unmet needs in hereditary angioedema management remain for patients not having adequate response, experiencing tolerability issues, and/or a high treatment burden.[9,13,14] Most long-term prophylaxis treatments and compounds in development require parenteral administration. Availability of orally administered therapies represents a substantial unmet need for patients with hereditary angioedema.[9,13,14] Oral treatments used for long-term prophylaxis include the plasma kallikrein inhibitor berotralstat, attenuated androgens, and antifibrinolytics.[7–9,12] In a placebo-controlled phase 3 trial, daily berotralstat 150 mg reduced the mean attack rate by 44·2% compared with placebo and had non-significant effects on patient-reported health-related quality of life measured using AE-QoL.[26] Phase 3 trials of prophylactic drugs administered parenterally have shown mean monthly attack rate reductions relative to placebo in the range of 55–89% and, when assessed, significant effects on AE-QoL.[22–25,27] Management guidelines do not recommend attenuated androgens and antifibrinolytics as first-line treatment options for hereditary angioedema, unless other options are unavailable, due to the risk of serious adverse effects with androgens and inferior efficacy data for antifibrinolytics.[3,8,12] Thus, developing oral prophylactic treatments with an efficacy comparable to that of injectable therapies and without tolerability and safety issues is a key objective for novel therapeutic options.[9,14]

Limitations of this trial include the small sample size of patients, all of whom were White, and some imbalances in sex between treatment groups, which can be expected in a phase 2 trial. Descriptive statistical tests were used to compare treatment groups for secondary endpoints and patient-reported outcomes. Also noteworthy is that this study was a proof-of-concept trial with a short duration compared with most phase 3 trials for long-term prophylaxis, and the immediate-release capsule formulation was used, which is the formulation being primarily developed for on-demand treatment use, administered twice daily as a proof-of-concept for prophylactic use of deucrictibant. However, these limitations are anticipated to be addressed in a larger and longer global phase 3 trial (NCT06669754) using an extended-release tablet formulation, intended for prophylactic use, allowing for once-daily dosing of deucrictibant 40 mg, with the possibility that the single daily administration could be associated with additional benefits with regards to patient experience and treatment adherence.

Together with the findings from the RAPIDe-1 trial for on-demand treatment, results of the CHAPTER-1 trial for prophylaxis confirm the pivotal role of bradykinin signalling as a causative mediator of swelling in

hereditary angioedema. They also provide evidence that, as a first-in-class oral antagonist of the bradykinin B2 receptor, deucrictibant has the potential to be the first orally bioavailable molecule for both the prevention and treatment of hereditary angioedema attacks.

Additionally, results from CHAPTER-1[29,30] are consistent with those of pilot studies in acquired angioedema due to C1 inhibitor deficiency, suggesting that therapeutic indications of bradykinin B2 receptor antagonism and deucrictibant could include other subtypes of bradykinin-mediated angioedema, for which no treatments are currently approved. In conclusion, these phase 2 results support further investigation of the efficacy and safety of deucrictibant in a phase 3 trial of prophylaxis against hereditary angioedema attacks.

Contributors

PL, JK, and AL contributed to study conceptualisation and study design, funding acquisition, investigation, method, project administration, resources, supervision, and reviewed and provided input on the manuscript. MAR and EA-P contributed to study conceptualisation and study design. EA-P, MS, AV, MC, MG, SG, SK-A, TK, WHY, JA, FA, HC, NC, EE, MDG, PG, MM, MEM, MDT, HJW, AZ, and MAR were investigators in the clinical trial. RC, SM, JL, and LZ contributed to the formal analysis, data curation, data validation, and data visualisation. MAR, RC, LZ, JL and PL had access to the raw data and MAR and LZ verified the data. All authors contributed to data interpretation, and reviewing and editing the manuscript. All authors had full access to all the data in the study. All authors approved the manuscript and assume responsibility for the content provided.

Declaration of interests

EA-P has received fees as a speaker and/or consultant from Astria, BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, and Takeda and grants from CSL Behring and Takeda. MS has received fees as a speaker and or/consultant from BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Takeda. AV has received consultant, speaker, and personal fees from AstraZeneca, Berlin–Menarini Group, CSL Behring, KalVista, Novartis, Pharming, Sobi, and Takeda and was an investigator for Pharvaris. MC has received grant research support and/or speaker or consultancy fees from BioCryst, CSL Behring, KalVista, Pharming, Sobi, and Takeda; received funding to attend conferences or educational events from CSL Behring, Menarini, MSD, Novartis, Pharming, and Takeda; and is or has been a clinical trial and/or registry investigator for BioCryst, CSL Behring, KalVista, Novartis, Pharming, Pharvaris, Takeda, UCB, and Otsuka. MG has received travel and conference attendance support from CSL Behring; is a member of the immunology clinical reference group; and has done clinical trial work for BioCryst and Novartis. SG has received funding to attend conferences and other educational events; acted as medical advisor or speaker; received donations to her departmental fund; and received financial and other assistance for patient care projects and/or participated in clinical trials with Baxter, CSL Behring, Dyax, Grifols, Pharming–Swedish Orphan, Takeda, and ViroPharma. SK-A is chief and/or principal investigator for BioCryst, Biotest, CSL Behring, Ionis, KalVista, Otsuka pharmaceuticals, Pharvaris, and Takeda; has received honorarium for consulting work from BioCryst, Biotest, CSL Behring, Ionis, KalVista, Otsuka pharmaceuticals, Pharvaris, and Takeda; and has participated on advisory boards organised by BioCryst, Biotest, CSL Behring, Ionis, KalVista, Otsuka pharmaceuticals, Pharvaris, and Takeda. TK has received research grants and/or speaker or consultancy fees from BioCryst, CSL Behring, KalVista, Otsuka, Pharvaris, Sanofi–Regeneron, and Takeda and is or was an investigator in clinical studies for BioCryst, CSL Behring, KalVista, Otsuka, Pharvaris, Sanofi–Regeneron, and Takeda. WHY is a member of advisory boards for Blueprint, BioCryst, Celldex, CSL Behring, Intellia, Merck, Novartis, Sanofi, and Takeda; has received speaker fees from AstraZeneca, Merck, Novartis, and Takeda; research grants from Aimmune Therapeutics, ALK Abello, AnaptysBio, Areteia, Aslan, AstraZeneca, Astria, BioCryst, Blueprint, Bristol Myers, Celgene, Celldex, CSL Behring, DBV Technologies, Dermira, Eli Lilly, Escient, Galderma, Genentech, GSK, Glenmark, Haleon, Incyte, Intellia, Ionis, Moderna, Novartis, Novavax, Pharvaris, Pharming, Providence, RAPT Therapeutics, Regeneron, Roche, Sanofi, Stallergenes, Takeda, Upstream Bio, and VBI Vaccines; is a medical advisor (volunteer) for the patient organisation Hereditary Angioedema Canada; and is a member of Angioedema Centers of Reference and Excellence, Blueprint, Celldex, and Intellia. 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RC is an employee of RC Consultancy; a consultant to Pharvaris; and holds stocks in Pharvaris. SM is an employee of Mulders Clinical Consulting; a consultant to Pharvaris; and holds stocks in Pharvaris. JL, LZ, and PL are employees of Pharvaris and hold stocks in Pharvaris. JK is an employee of JCK Consult; a consultant to Pharvaris; and holds stocks or stock options in Pharvaris. AL is an employee of GrayMatters Consulting; a consultant to Pharvaris; holds stocks or stock options in Pharvaris; and is an advisor to Kosa Pharma. MAR has received research grant support, consultancy fees, speaker fees, and/or clinical trial fees from Astria, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, and Takeda.

Data sharing

The data in this study will not be made available as the study is still ongoing. Once the study is completed Pharvaris will consider requests from qualified scientific and medical researchers to share de-identified participant data that underlie results in this Article. Data requests will be considered from 6 months after marketing approval of the study drug in both the USA and European Union. Supporting documents, including the study protocol and statistical analysis plan, can also be requested. Proposed research should seek to answer a previously unanswered important medical or scientific question and any data-sharing requests should reflect those important questions. Any applicable country-specific privacy and other laws and regulations will be considered and might

prevent sharing of data. For further information on the process and requirements for submitting a data-sharing request, please contact Pharvaris at DSR@Pharvaris.com.

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