Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Timothy J Craig, Avner Reshef, H Henry Li, Joshua S Jacobs, Jonathan A Bernstein, Henriette Farkas, William H Yang, Erik S G Stroes, Isao Ohsawa, Raffi Tachdjian, Michael E Manning, William R Lumry, Inmaculada Martinez Saguer, Emel Aygören-Pürsün, Bruce Ritchie, Gordon L Sussman, John Anderson, Kimito Kawahata, Yusuke Suzuki, Petra Staubach, Regina Treudler, Henrike Feuersenger, Fiona Glassman, Iris Jacobs, Markus Magerl

Summary

Background Hereditary angioedema is a rare and potentially life-threatening genetic disease that is associated with kallikrein–kinin system dysregulation. Garadacimab (CSL312), a novel, fully-human monoclonal antibody that inhibits activated factor XII (FXIIa), is being studied for the prevention of hereditary angioedema attacks. The aim of this study was to evaluate the efficacy and safety of once-monthly subcutaneous administrations of garadacimab as prophylaxis for hereditary angioedema.

Methods VANGUARD was a pivotal, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial that recruited patients (aged ≥12 years) with type I or type II hereditary angioedema across seven countries (Canada, Germany, Hungary, Israel, Japan, the Netherlands, and the USA). Eligible patients were randomly assigned (3:2) to receive garadacimab or placebo for 6 months (182 days) by an interactive response technology (IRT) system. Randomisation was stratified by age (≤17 years *vs* >17 years) and baseline attack rate (1 to <3 attacks per month *vs* ≥3 attacks per month) for the adult group. The randomisation list and code were kept by the IRT provider during the study, with no access by site staff and funding representatives. All patients and investigational site staff, and representatives from the funder (or their delegates) with direct interaction with the study sites or patients, were masked to treatment assignment in a double-blind fashion. Randomly assigned patients received a 400-mg loading dose of subcutaneous garadacimab as two 200-mg injections or volume-matched placebo on day 1 of the treatment period, followed by five additional self-administered (or caregiver-administered) monthly doses of 200-mg subcutaneous garadacimab or volume-matched placebo. The primary endpoint was the investigator-assessed time-normalised number of hereditary angioedema attacks (number of hereditary angioedema attacks per month) during the 6-month treatment period (day 1 to day 182). Safety was evaluated in patients who received at least one dose of garadacimab or placebo. The study is registered with the EU Clinical Trials Register, 2020-000570-25 and ClinicalTrials.gov, NCT04656418.

Findings Between Jan 27, 2021, and June 7, 2022, we screened 80 patients, 76 of whom were eligible to enter the run-in period of the study. Of 65 eligible patients with type I or type II hereditary angioedema, 39 were randomly assigned to garadacimab and 26 to placebo. One patient was randomly assigned in error and did not enter the treatment period (no dose of study drug received), resulting in 39 patients assigned to garadacimab and 25 patients assigned to placebo being included. 38 (59%) of 64 participants were female and 26 (41%) were male. 55 (86%) of 64 participants were White, six (9%) were Asian (Japanese), one (2%) was Black or African American, one (2%) was Native Hawaiian or Other Pacific Islander, and one (2%) was listed as other. During the 6-month treatment period (day 1 to day 182), the mean number of investigator-confirmed hereditary angioedema attacks per month was significantly lower in the garadacimab group (0·27, 95% CI 0·05 to 0·49) than in the placebo group (2·01, 1·44 to 2·57; p<0·0001), corresponding to a percentage difference in means of –87% (95% CI –96 to –58; p<0·0001). The median number of hereditary angioedema attacks per month was 0 (IQR 0·00–0·31) for garadacimab and 1·35 (1·00–3·20) for placebo. The most common treatment-emergent adverse events were upper-respiratory tract infections, nasopharyngitis, and headaches. FXIIa inhibition was not associated with an increased risk of bleeding or thromboembolic events.

Interpretation Monthly garadacimab administration significantly reduced hereditary angioedema attacks in patients aged 12 years and older compared with placebo and had a favourable safety profile. Our results support the use of garadacimab as a potential prophylactic therapy for the treatment of hereditary angioedema in adolescents and adults.

Funding CSL Behring.

Published **Online** February 28, 2023 https://doi.org/10.1016/S0140-6736(23)00350-1

See **Online/Comment** https://doi.org/10.1016/S0140-6736(23)00092-2

Allergy, Asthma and Immunology, Department of Medicine and Pediatrics, Penn State University, Hershey, PA, USA (Prof T J Craig DO); **Allergy, Immunology & Angioedema Center, Barzilai University Hospital, Ashkelon, Israel** (A Reshef MD); **Institute for Asthma and Allergy, Chevy Chase, MD, USA** (H H Li MD); **Allergy & Asthma Clinical Research, Walnut Creek, CA, USA** (J S Jacobs MD); **University of Cincinnati, Department of Internal Medicine Division of Rheumatology, Allergy and Immunology and the Bernstein Clinical Research Center Cincinnati, Cincinnati, OH, USA** (Prof J A Bernstein MD); **Department of Internal Medicine and Haematology, Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary** (Prof H Farkas PhD); **Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, ON, Canada** (W H Yang MD); **Department of Vascular Medicine, Amsterdam UMC, Amsterdam, Netherlands** (Prof E S G Stroes PhD); **Department of Nephrology, Saiyu Soka Hospital, Saitama, Japan** (I Ohsawa MD); **Division of Allergy & Clinical Immunology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA** (R Tachdjian MD); **Allergy,**

Asthma & Immunology Associates, Ltd, Internal Medicine, UA College of Medicine, Phoenix, Phoenix, AZ, USA (M E Manning MD); AARA Research Center, Dallas, TX, USA (W R Lumry MD); HZRM Haemophilia Center Rhein Main, Mörfelden-Walldorf, Germany (I Martinez Saguer MD); Klinikum der Johann Wolfgang-Goethe Universität, Klinik für Kinder- und Jugendmedizin, Frankfurt, Germany (E Aygören-Pürsün MD); Division of Hematology, Department of Medicine, University of Alberta, Edmonton, AB, Canada (Prof B Ritchie MD); Gordon Sussman Clinical Research Inc and Department of Clinical Immunology and Allergy, St Michael's Hospital, Toronto, ON, Canada (G L Sussman MD); AllerVie Clinical Research, Birmingham, AL, USA (J Anderson MD); St Marianna University School of Medicine, Kawasaki-shi, Kanagawa, Japan (K Kawahata MD); Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan (Y Suzuki MD); Department of Dermatology and Allergy, University Medical Center, Mainz, Germany (P Staubach MD); University Leipzig Medical Faculty, Department of Dermatology, Venereology and Allergology, Leipzig Interdisciplinary Center for Allergology—CAC, Leipzig, Germany (R Treudler MD); CSL Behring Innovation GmbH, Marburg, Germany (H Feuersenger PhD); CSL Behring, King of Prussia, PA, USA (F Glassman PhD, I Jacobs MD); Institute of Allergology, Charité–Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany (Prof M Magerl MD); Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany (Prof M Magerl)

Research in context

Evidence before this study

Despite advances in the management of hereditary angioedema, prophylactic treatments often require frequent dosing and largely do not provide early or sustained protection against attacks. There is an unmet need for more convenient, well-tolerated, prophylactic treatments that show early and sustained efficacy in reducing the number and severity of hereditary angioedema attacks, with a rapid onset of protection. We searched PubMed with the term "hereditary angioedema" and filtered the results for articles that described randomised trials published between Jan 1, 2018, and Dec 31, 2022, with no language restrictions. During this period, 16 randomised trials were published. Of these, seven involved C1-esterase inhibitor concentrates, seven investigated the kallikrein inhibitors avoralstat, berotralstat, and lanadelumab, one investigated the plasma prekallikrein inhibitor donidalorsen, and one phase 2 trial investigated the anti-activated factor XII (FXIIa) inhibitor garadacimab. The phase 2 study of garadacimab, a novel first-in-class fully human monoclonal antibody that targets FXIIa, showed a significant reduction in the number of hereditary angioedema attacks per month with garadacimab compared with placebo over 12 weeks, with an early onset of efficacy. Post-hoc pharmacokinetic analyses highlighted that increasing concentrations of garadacimab appeared to decrease the relative risk of attacks, with no additional efficacy benefit in patients who received 600 mg compared with those who received 200 mg. Our phase 3 study was done to confirm the efficacy and safety of once-monthly 200 mg garadacimab in patients with type I or type II hereditary angioedema.

Added value of this study

In this double-blind, randomised, placebo-controlled, phase 3 trial, once-monthly subcutaneous administrations of garadacimab produced clinically meaningful outcomes in most patients. Over 6 months, prophylaxis with garadacimab significantly lowered the number of hereditary angioedema attacks compared with placebo (0·27 attacks per month with garadacimab *vs* 2·01 attacks per month with placebo; p<0·0001), corresponding to a reduction in means of 87%. Patients treated with garadacimab had a 91% reduction in the number of hereditary angioedema attacks per month compared with the run-in period, which was a significantly greater reduction than that of patients receiving placebo (20%). Additionally, patients treated with garadacimab had a 90% reduction in the mean number of moderate or severe hereditary angioedema attacks per month compared with patients who received placebo. Notably, almost three-quarters of patients who received garadacimab were attack-free during the initial 3 months of treatment compared with less than 10% of patients who received placebo (p<0·0001), and the majority (62%) were attack-free during the entire 6 months of treatment compared with no patients who received placebo (p<0·0001).

Implications of all the available evidence

We found that once-monthly subcutaneous garadacimab provided early and sustained protection from hereditary angioedema attacks, with a favourable safety profile. These results support the use of garadacimab as a potential prophylactic therapy for patients with hereditary angioedema.

Introduction

Hereditary angioedema is a rare autosomal dominant disorder characterised by recurrent, painful angioedema episodes (attacks) that most commonly affect the skin, face, extremities, trunk, genitals, and mucous membranes of the gastrointestinal tract and upper airways. Attacks are unpredictable and potentially life-threatening, and negatively affect patient quality of life.[1–6] Hereditary angioedema attacks are caused by spontaneous, uncontrolled activation of the plasma kallikrein–kinin system and overproduction of the vasoactive peptide bradykinin, which increases endothelial permeability and causes subsequent extravasation of fluids into interstitial tissues.[7–9] Activation of factor XII (FXII) initiates the kallikrein–kinin system, leading to bradykinin formation.[7–9] In healthy individuals, the kallikrein–kinin system is tightly regulated by C1-esterase inhibitor (C1-INH);[3,7–10] most cases of hereditary angioedema are associated with a deficiency (type I) or dysfunction (type II) in C1-INH caused by mutations in the C1-INH gene (*SERPING1*).[1,2]

Approved prophylactic treatments for hereditary angioedema aim to compensate for C1-INH deficiency (C1-INH concentrates) or inhibit bradykinin release by targeting plasma kallikrein.[1,11] These treatments often require frequent dosing regimens (eg, twice-weekly administrations with C1-INH, administrations every 2 weeks with lanadelumab),[12,13] and in clinical trials have shown a delay in reaching maximum efficacy upon reaching steady-state concentrations (ie, 14 days or 70 days from the start of treatment, respectively), with most patients still having attacks in the first 2 months after treatment initiation.[12,13] Therefore, there is a need for new, well-tolerated, effective therapies, with enhanced convenience and early and sustained protection from hereditary angioedema attacks. The pivotal role of activated FXII (FXIIa) in initiating the kallikrein–kinin cascade provides a strong rationale for therapeutic targeting to prevent the downstream production of bradykinin that leads to hereditary angioedema attacks.

Garadacimab (CSL312), a first-in-class, fully-human monoclonal IgG4 antibody against FXIIa, was shown to prevent bradykinin formation in plasma samples from patients with hereditary angioedema with C1-INH deficiency.[14] In a randomised, placebo-controlled, phase 2 trial, garadacimab significantly reduced the number of hereditary angioedema attacks per month compared with placebo over 12 weeks and provided the first clinical evidence of FXIIa inhibition as a novel

strategy for hereditary angioedema prophylaxis.[15] Here, the efficacy and safety of subcutaneous garadacimab were investigated in a 6-month, randomised, double-blind, placebo-controlled, pivotal phase 3 trial (VANGUARD) in patients with type I or type II hereditary angioedema.

Methods

Study design and participants

VANGUARD was a randomised, double-blind, placebo-controlled, pivotal phase 3 trial to investigate the efficacy and safety of an initial loading dose of subcutaneous garadacimab (two 200-mg injections) followed by once-monthly 200 mg garadacimab in adolescents and adults with a laboratory-confirmed diagnosis of type I or type II hereditary angioedema. Considering that maximum efficacy and a favourable safety profile were observed in the phase 2 trial, a once-monthly 200-mg maintenance dose of garadacimab was believed to be the optimal dose for a phase 3 trial in a larger population.[15] The trial was run globally across 28 centres in Canada (four centres), Germany (six centres), Hungary (one centre), Israel (one centre), Japan (six centres), the Netherlands (one centre), and the USA (nine centres). This trial was done and documented in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. All patients or caregivers provided written informed consent (or assent for minors) before screening. This study was done under a US Food and Drug Administration Biological License Application and documented in accordance with the applicable regulatory guidelines and requirements. The clinical trial protocol and informed consent forms were approved by an authorised institutional review board or independent ethics committee (La Jolla, CA, USA). For Japanese sites only, the head of the study site submitted a written report to the institutional review board that detailed all safety-related information reported by the funding source. Biostatistical analysis was done by an independent third party (appendix p 2).

Potentially eligible patients were aged 12 years or older at screening (adolescents: ≥12 years ≤17 years, adults: >17 years), with a confirmed diagnosis of type I or type II hereditary angioedema based on the following criteria: documented clinical history consistent with hereditary angioedema, C1-INH functional activity of 50% or less (reference range 70–130% of normal plasma), and a C4 antigen concentration below the lower limit of the reference range (0·16–0·38 mg/mL;[16] appendix p 3). Additionally, patients must have had at least three hereditary angioedema attacks during the 3 months before screening (or over 3 consecutive months before commencing any prophylactic therapy before screening). Eligible patients were required to willingly stop using long-term prophylactic hereditary angioedema treatments (eg, C1-INH replacement therapy, androgens, antifibrinolytics, or other small molecule medications), allowing for a washout period of at least 2 weeks before the start of the run-in period (appendix p 4). Routine hereditary angioedema prophylactic treatments were prohibited during the run-in period and the 6-month treatment period; on-demand therapies were permitted as per patient treatment plans.

Patients were excluded in cases of concomitant diagnosis of other forms of angioedema (eg, idiopathic, acquired, hereditary angioedema with normal C1-INH), preplanned major surgeries, and use of monoclonal antibodies within 3 months before the run-in period, garadacimab (in previous trials), or oestrogen-containing medications. After screening, patients were enrolled in a 1–2-month run-in period to confirm disease activity and baseline number of hereditary angioedema attacks per month.

A country feasibility assessment was done by the contract research organisation and patients were recruited by the study investigators of participating sites. Sex was captured (not gender) by self-reporting, with the options female, male, or unknown.

Following the 6-month treatment period, patients who completed the randomised, placebo-controlled period could enrol in the open-label extension period (EudraCT, 2020-003918-12; ClinicalTrials.gov, NCT04739059).

Corespondence to:
Prof Timothy J Craig, Allergy, Asthma and Immunology, Department of Medicine and Pediatrics, Penn State University, Hershey, PA 17033, USA
tcraig@pennstatehealth.psu.edu

See **Online** for appendix

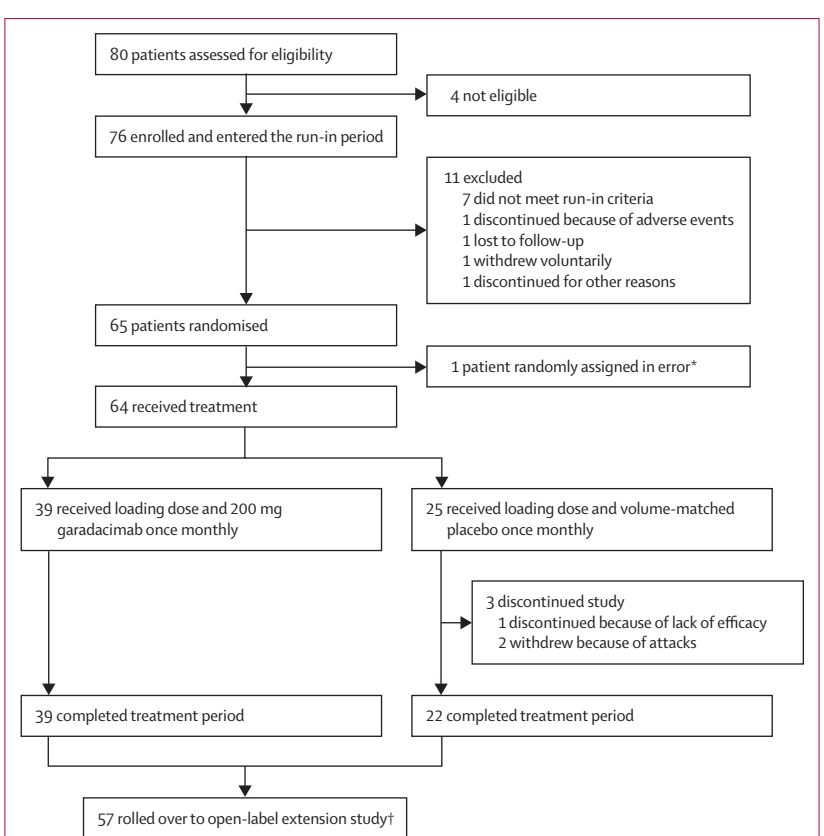


Figure 1: **Trial profile**
*One patient was randomly assigned via interactive response technology in error; the patient did not receive the loading dose at day 1 (number of patients per site enrolled is provided in the appendix p 13). †Four patients opted out of the open-label extension trial for personal reasons.

Randomisation and masking

Patients who had at least two hereditary angioedema attacks in the study run-in period (≥1 attack per month) were randomly assigned (3:2) to receive garadacimab or placebo by an interactive response technology (IRT) system (Suvoda; Conshohocken, PA, USA). Randomisation was stratified by age (≤17 years *vs* >17 years) and baseline attack rate (1 to <3 attacks per month *vs* ≥3 attacks per month) for the adult group. The randomisation list and code were kept by the IRT provider during the study, with no access by site staff and funding representatives. All patients and investigational site staff, and representatives from the funder (or their delegates) with direct interaction with the study sites or patients, were masked to treatment assignment in a double-blind fashion. In case of emergency, a patient's treatment could be revealed with the IRT by the investigator. To maintain masking, volume-matched doses of garadacimab and placebo were administered with indistinguishable prefilled syringes. The bioanalyst and pharmacokineticist responsible for the sample analysis, pharmacokinetics and pharmacodynamics, immunogenicity, and coagulation were not masked to treatment allocation and instructed not to disclose the randomisation schedule or any data.

	Garadacimab 200 mg group (n=39)	Placebo group (n=25)	Total (n=64)
Sex			
Female	24 (62%)	14 (56%)	38 (59%)
Male	15 (38%)	11 (44%)	26 (41%)
Age at screening, years	43·3 (17·5) [12–69]	37·8 (12·8) [14–62]	41·2 (15·9) [12–69]
BMI at screening, kg/m²	27·9 (6·0)	28·4 (7·6)	28·1 (6·6)
Race			
Asian (Japanese)	4 (10%)	2 (8%)	6 (9%)
Black or African American	0	1 (4%)	1 (2%)
Native Hawaiian or Other Pacific Islander	1 (3%)	0	1 (2%)
White	33 (85%)	22 (88%)	55 (86%)
Other	1 (3%)	0	1 (2%)
Hereditary angioedema type			
I	34 (87%)	22 (88%)	56 (88%)
II	5 (13%)	3 (12%)	8 (13%)
Patient age group at diagnosis, years			
≤17	18 (46%)	12 (48%)	30 (47%)
>17 to ≤40	18 (46%)	11 (44%)	29 (45%)
>40	3 (8%)	2 (8%)	5 (8%)
Patients on prophylactic therapy during the 3 months before screening*	14 (36%)	7 (28%)	21 (33%)
Number of hereditary angioedema attacks during the 3 months before screening or at the start of prophylaxis	8·6 (6·3–10·9)	9·3 (6·4–12·2)	8·9 (7·1–10·6)
Number of hereditary angioedema attacks during the run-in period	3·1 (2·4–3·7)	2·5 (2·1–2·9)	..
History of laryngeal attacks	21 (54%)	17 (68%)	38 (59%)
Location of hereditary angioedema attacks during the 3 months before screening†			
Cutaneous (extremities)	30 (77%)	20 (80%)	50 (78%)
Abdominal	30 (77%)	18 (72%)	48 (75%)
Facial	13 (33%)	8 (32%)	21 (33%)
Throat, larynx, or tongue	3 (8%)	2 (8%)	5 (8%)
Peripheral‡	1 (3%)	0	1 (2%)

Data are n (%), mean (SD) [range], mean (SD), or mean (95% CI). Garadacimab and placebo were administered every 4 weeks. *During the 3 months before entering the run-in period, all 21 (33%) patients receiving hereditary angioedema prophylaxis discontinued their prophylactic treatments, including C1 esterase inhibitor (subcutaneous or intravenous), berotralstat, lanadelumab, tranexamic acid, and danazol. †The full list of primary locations of hereditary angioedema attacks in the last 3 months before screening is available in the appendix (p 13). ‡As described by the investigator using the free text option in the patient's eDiary.

Table 1: **Baseline demographic and disease characteristics**

Procedures

Randomly assigned patients received a 400-mg loading dose of subcutaneous garadacimab as two 200-mg injections or volume-matched placebo on day 1 of the treatment period, followed by five additional self-administered (or caregiver-administered) monthly doses of 200-mg subcutaneous garadacimab or volume-matched placebo (appendix p 7). After self-administration training, the first three doses (including the 400-mg loading dose administered as two 200-mg injections of garadacimab or volume-matched placebo at day 1) were self-administered by patients or caregivers under the supervision of the investigator or delegate during site visits on days 1, 31, and 61. Subsequent doses could be self-administered once per month without supervision at scheduled times (days 91, 121, and 151). Patients were encouraged to record details of any symptoms of potential attacks in electronic diaries (eDiaries) and were invited to contact the trial site within 72 h after attack onset. Investigators confirmed attacks, attack severity, and adverse events (treatment period only) upon reviewing the eDiaries at site visits or by telephone call every 2 weeks throughout the run-in period. Detailed guidance provided to investigators for the assessment of hereditary angioedema attack severity is available in the appendix (p 4).

At the day 1 site visit, investigators confirmed eligibility to enter the treatment period and access to rescue medication, and did physical examinations, urinalysis, pregnancy testing, administration of the first dose of either placebo or garadacimab, blood draws (the before-dose blood draw was to be analysed for haematology, biochemistry, coagulation parameters [eg, activated partial thromboplastin time], future assessments of hereditary angioedema biomarkers [adults only], and immunogenicity; blood draws were analysed for pharmacokinetics and pharmacodynamics [eg, garadacimab concentrations, FXII concentration, and FXIIa-mediated kallikrein activity]), review of eDiaries, and review of concomitant medication. Blood draws for pharmacokinetics and pharmacodynamics and immunogenicity assessments were done at each site visit. Pharmacokinetic and immunogenicity analyses were done using established protocols[15] (appendix p 5). These assessments,

and some of the day 1 assessments, were done at scheduled times as detailed in the appendix (pp 10–12). Throughout the 6-month treatment period, follow-up visits occurred at study sites every 2 weeks from day 1.

Any unfavourable and unintended sign (including an abnormal, clinically significant laboratory finding), disease, or symptom temporally associated with study treatment was considered to be an adverse event and was recorded regardless of relatedness to either garadacimab or placebo. Thromboembolic events, bleeding events, and hypersensitivity or anaphylaxis were classified as adverse events of special interest. Any adverse events with an onset time or date on or after the first injection of study treatment were considered to be treatment-emergent adverse events. Adverse events were coded according to System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (version 25.0). All adverse events were assessed by the investigator as either related or not related to garadacimab, based on a plausible clinical or pathophysiological context or temporal relationship (eg, the event being related by time to treatment administration or termination), prior adverse reactions to similar products, or being treatment related.

Outcomes

The primary endpoint was the investigator-assessed time-normalised number of hereditary angioedema attacks (number of hereditary angioedema attacks per month) during the 6-month treatment period (day 1 to day 182). Three secondary efficacy endpoints were tested in the following hierarchical order: the percentage reduction in the number of hereditary angioedema attacks per month compared with placebo (day 1 to day 182), the number of patients who were attack free through to day 91, and the percentage of patients rating therapy as "good" or better with the Subject's Global Assessment of Response to Therapy (SGART) at day 182. The additional secondary efficacy endpoints were attack-rate reductions compared with the run-in period (defined as ≥50%, ≥70%, ≥90%, or 100% reduction) and attack rates at prespecified timepoints (during the first and second 3-month treatment period), number of attacks per month requiring rescue medication, and number of moderate or severe attacks per month.

Secondary safety endpoints were adverse events, including adverse events of special interest (ie, anaphylaxis, thromboembolic, or abnormal bleeding events) and serious adverse events, concentrations of anti-garadacimab antibodies, and clinically significant abnormalities in laboratory assessments. Prespecified exploratory endpoints included the time to first attack after days 1 and 14, and garadacimab concentrations at scheduled timepoints during the treatment period (days 1 [start of treatment period], 31, 61, 91, 121, 151, and 182 [end of treatment period]) and at follow-up visit (day 242). We also report the Angioedema Quality-of-Life (AE-QoL)

	Garadacimab 200 mg group (n=39)	Placebo group (n=25)
Total number of hereditary angioedema attacks (day 1 to day 182)	63	264
Primary endpoint (day 1 to day 182)		
Mean (95% CI) number of hereditary angioedema attacks per month	0·27 (0·05 to 0·49)	2·01 (1·44 to 2·57)
p value *vs* placebo (two-sided Wilcoxon test, hierarchical testing H01)*	<0·0001	..
Median (IQR) number of hereditary angioedema attacks per month	0 (0·0 to 0·31)	1·35 (1·00 to 3·20)
Least squares mean (95% CI) number of hereditary angioedema attacks per month†	0·22 (0·11 to 0·47)	2·07 (1·49 to 2·87)
Percentage difference *vs* placebo (95% CI)	–89% (–95 to –76)	..
Secondary endpoints		
Percentage difference in the mean number of hereditary angioedema attacks per month *vs* placebo (95% CI) during entire 6-month treatment period	–87% (–96 to –58)	..
p value *vs* placebo (two-sided Wilcoxon test, hierarchical testing H02)*	<0·0001	..
Patients with no attacks during the first 3 months of the treatment period (months 1–3)	28 (72%)	2 (8%)
p value *vs* placebo (Fisher exact test, nominal p value; hierarchical testing H03)*	<0·0001	..
Patients with no attacks during the second 3 months of the treatment period (months 4–6)	27 (69%)	2 (9%)
p value *vs* placebo (Fisher exact test, nominal p value)	<0·0001	..
Subject's Global Assessment of Response to Therapy at visit day 182		
"Good" or better‡	31/38 (82%)	8/24 (33%)
p value *vs* placebo (χ^2 test, hierarchical testing H04)*	<0·0001	..
Other secondary endpoints		
Percentage reduction in monthly hereditary angioedema attacks in the treatment period *vs* the run-in period (day 1 to day 182), mean (95% CI)	91% (83·4 to 97·9)	20 (2·2 to 38·2)
p value *vs* placebo (two-sided Wilcoxon test, nominal p value)	<0·0001	..
Patients responding to treatment *vs* run-in period (day 1 to day 182)		
≥50% reduction in the number of hereditary angioedema attacks per month	37 (95%)	8 (33%)
≥70% reduction in the number of hereditary angioedema attacks per month	36 (92%)	4 (17%)
≥90% reduction in the number of hereditary angioedema attacks per month	29 (74%)	2 (8%)
Patients with no attacks (day 1 to day 182)	24 (62%)	0
p value *vs* placebo (Fisher exact test, nominal p value)	<0·0001	..
Number of hereditary angioedema attacks requiring on-demand treatment per month		
Entire treatment period (6 months), mean (95% CI)	0·23 (0·02 to 0·45)	1·86 (1·26 to 2·46)
Percentage difference in means *vs* placebo	–88%	..
p value *vs* placebo (two-sided Wilcoxon test, nominal p value)	<0·0001	..
Entire treatment period (6 months), median (IQR)	0·00 (0·0 to 0·17)	1·35 (0·67 to 3·07)

(Table 2 continues on next page)

	Garadacimab 200 mg group (n=39)	Placebo group (n=25)
(Continued from previous page)		
First half of the treatment period (months 1–3), mean (95% CI)	0·24 (0·00 to 0·48)	1·76 (1·18 to 2·35)
p value *vs* placebo (two-sided Wilcoxon test, nominal p value)	<0·0001	..
Second half of treatment period (months 4–6), mean (95% CI)	0·23 (0·03 to 0·43)	1·80 (1·08 to 2·52)
p value *vs* placebo (two-sided Wilcoxon test, nominal p value)	<0·0001	..
Number of moderate or severe hereditary angioedema attacks per month (day 1 to day 182), mean (95% CI)	0·13 (0·03 to 0·22)	1·35 (0·86 to 1·84)
Percentage difference *vs* placebo	–90%	..
p value *vs* placebo (two-sided Wilcoxon test, nominal p value)	<0·0001	..
Patients with at least one hereditary angioedema attack of maximum severity defined below (day 1 to day 182)§		
Severe	5 (13%)	10 (42%)
Moderate	5 (13%)	12 (50%)
Mild	5 (13%)	2 (8%)

Data are n or n (%), unless otherwise indicated. One (4%) patient in the placebo group stayed less than 30 days in the treatment period and was excluded from the analysis, as per the clinical trial protocol. In the placebo group, 24 patients were included in the analysis for the first half of the treatment period (months 1–3) and 22 in the second half of the treatment period (months 4–6). *Full details on hierarchical testing are available in the appendix (p 5). †Sensitivity analysis using a generalised linear model, assuming Poisson distribution; to report the mean hereditary angioedema attack rate per month, the received estimates were transformed by the exponential function and scaled by time. ‡Percentages were calculated with the number of patients with available data for Subject's Global Assessment Response to Therapy at day 182 (38 for garadacimab and 24 for placebo). §Percentages were calculated with the number of patients in the treatment period for at least 30 days as the denominator (39 for garadacimab and 24 for placebo).

Table 2: **Primary endpoint and secondary efficacy endpoints**

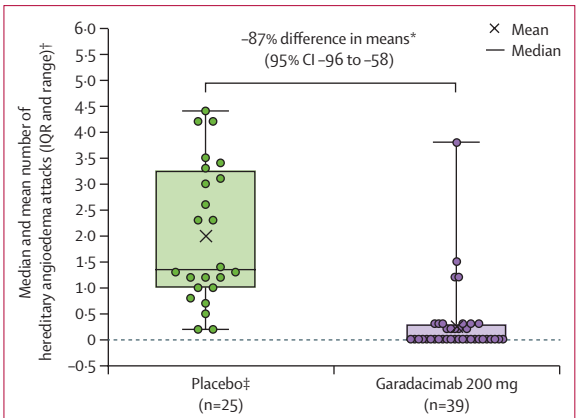


Figure 2: **Mean and median number of monthly attacks during the 6-month treatment period**

*p<0·0001; two-sided Wilcoxon test (hierarchical testing H01). †The shaded boxes and error bars represent IQRs and minimum and maximum values, respectively; each dot represents the patient's mean number of hereditary angioedema attacks per month during the treatment period. ‡One patient in the placebo group with less than 30 days of treatment was excluded from analyses, as prespecified in the clinical trial protocol.

questionnaire total score at day 31 and day 182 (appendix p 5). FXIIa-mediated kallikrein activity and full QoL data will be reported elsewhere.

Statistical analysis

A sample size of 60 patients, including five adolescents, was estimated to ensure 6-month trial completion by at least 40 patients to detect a treatment difference in the time-normalised number of investigator-confirmed attacks between garadacimab and placebo with approximately 90% power using a two-sided Wilcoxon test (α level 0·05). A monthly attack rate of 0·3125 and 1·3 was assumed for patients who received garadacimab or placebo, respectively, as per previous findings.[15] The intention-to-treat analysis (ie, all randomly assigned patients) was used for efficacy analyses. As a sensitivity analysis across the 6-month treatment period, attack rates were compared between treatment groups using a generalised linear model for count data, assuming a Poisson distribution. The model included treatment (categorical) and the baseline attack rate during the run-in period (continuous) as covariates and accounted for overdispersion. There were no deviations from the protocol affecting the statistical analysis, quality of the data, or patient safety.

To control the overall type I error rate, we applied a hierarchical testing procedure across the primary and three secondary efficacy endpoints according to prespecified hypotheses. The primary endpoint (H01) was tested using a Wilcoxon test. Hierarchically tested secondary endpoints were tested using a Wilcoxon test (H02), Fisher exact test (H03), and χ^2 test (H04). Testing was done at the two-sided 0·05 α level. All other secondary and exploratory endpoints were tested in an exploratory manner at a two-sided 0·05 α level not adjusted for multiplicity (referred to as nominal p value) by use of Wilcoxon or Fisher exact tests.

The safety population included all randomly assigned patients who received at least one treatment dose. Pharmacokinetic and pharmacodynamic analyses were done in patients in the safety analysis set for whom at least one measurement was obtained. Because of the COVID-19 pandemic, adverse events related to COVID-19 vaccine administration were identified and recorded via Medical Dictionary for Regulatory Activities coding (version 25.0).

Continuous variables are presented using mean values, with corresponding 95% CIs or SDs, or median (IQR). We considered p values of 0·05 or less to be statistically significant. The percentage difference in means was calculated as the difference between the mean number of hereditary angioedema attacks in the placebo group and garadacimab group, expressed as a percentage.

An independent data monitoring committee provided oversight (ie, independent statistical and clinical oversight). Statistical analyses were done with SAS

version 9.4. The study is registered with the EU Clinical Trials Register, 2020-000570-25 and ClinicalTrials.gov, NCT04656418.

Role of the funding source

The funder of the study contributed to the study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit for publication.

Results

Between Jan 27, 2021, and June 7, 2022, we screened 80 patients, 76 of whom were eligible to enter the run-in period of the study. Of 65 eligible patients with type I or type II hereditary angioedema, 39 were randomly assigned to garadacimab and 26 to placebo (figure 1). One patient was randomly assigned in error and did not enter the treatment period (no dose of study drug received), resulting in 39 patients assigned to garadacimab and 25 patients assigned to placebo being included in the intention-to-treat set. The baseline demographic and clinical characteristics of patients were similar across treatment groups (table 1; appendix p 13). 38 (59%) of 64 participants were female and 26 (41%) were male. 55 (86%) of 64 participants were White, six (9%) were Asian (Japanese), one (2%) was Black or African American, one (2%) was Native Hawaiian or Other Pacific Islander, and one (2%) was listed as other. The mean age of the six adolescents included in the study was 14·5 years (SD 1·8). During the 3 months before entering the run-in period, all 21 (33%) patients who were receiving hereditary angioedema prophylaxis discontinued their prophylactic treatments; 14 patients in the garadacimab group received either complement C1-INH (intravenous or subcutaneous; six patients), berotralstat dihydrochloride (four patients), tranexamic acid (two patients), danazol (one patient), or landelumab (one patient), and seven patients in the placebo group received either berotralstat dihydrochloride (three patients), complement C1-INH (two patients), tranexamic acid (one patient), or danazol (one patient). 61 (95%) of 64 patients received all six treatment doses; three (5%) patients in the placebo group discontinued treatment because of the high number of attacks and no patients in the garadacimab group discontinued treatment. As of June 7, 2022 (the study end date), 57 (89%) of 64 patients had enrolled in the open-label extension study.

During the 6-month treatment period (day 1 to day 182), the mean number of investigator-confirmed hereditary angioedema attacks per month was significantly lower in the garadacimab group (0·27, 95% CI 0·05 to 0·49) than in the placebo group (2·01, 1·44 to 2·57; p<0·0001; table 2), corresponding to a percentage difference in means of –87 (95% CI –96 to –58; p<0·0001; figure 2). The median number of hereditary angioedema attacks per month was 0 (IQR 0·00–0·31) for garadacimab and 1·35 (1·00–3·20) for placebo. When adjusted for the baseline number of attacks, the difference in the least squares mean monthly number of attacks was –89% (95% CI –95 to –76). 28 (72%) of 39 patients in the garadacimab group had no attacks over the first 3 months of the treatment period versus two (8%) of 24 patients in the placebo group (p<0·0001). 27 (69%) of 39 patients in the garadacimab group had no attacks over the second 3 months of the treatment period compared with two (9%) of 22 patients in the placebo group (p<0·0001; table 2). 24 (62%) of 39 patients had no attacks over the entire treatment period in the garadacimab group, compared with no patients in the placebo group (table 2). Of the patients with available responses at day 182, 31 (82%) of 38 patients in the garadacimab group rated the response to treatment (SGART) as "good" or better and 25 (66%) of 38 patients rated the response to treatment as "excellent" compared with eight (33%) and three (13%) of 24 patients in the placebo group, respectively (appendix pp 8, 14). One (3%) and three (8%) of 38 patients in the garadacimab group rated the response to treatment as "none" or "poor" (indicating no or worsening response), compared with ten (42%) and four (17%) of 24 patients in the placebo group, respectively. The patient who assessed treatment response as "none" in the garadacimab group had no attacks during the 6-month treatment period. The three patients treated with garadacimab who assessed treatment response as "poor" had at least a 50% attack-rate reduction (51%, 83%, and 93%) throughout the treatment period, and continued their once-monthly garadacimab treatment in the open-label extension study.

The baseline mean numbers of hereditary angioedema attacks per month for the garadacimab group (3·1, 95% CI 2·4–3·7) and placebo group (2·5, 2·1–2·9) in the run-in period were similar. Compared with baseline, patients in the garadacimab group had a 91% mean reduction in attacks (95% CI 83–98), whereas patients in the placebo group had a 20% mean reduction in attacks (2–38). 29 (74%) of 39 patients in the garadacimab group versus two (8%) of 24 evaluable patients in the placebo group had a 90% or greater reduction in the number of monthly

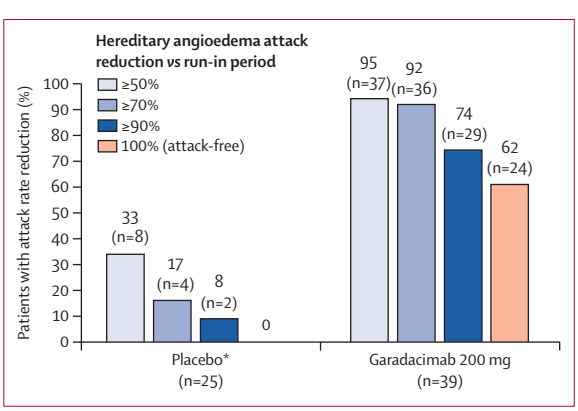
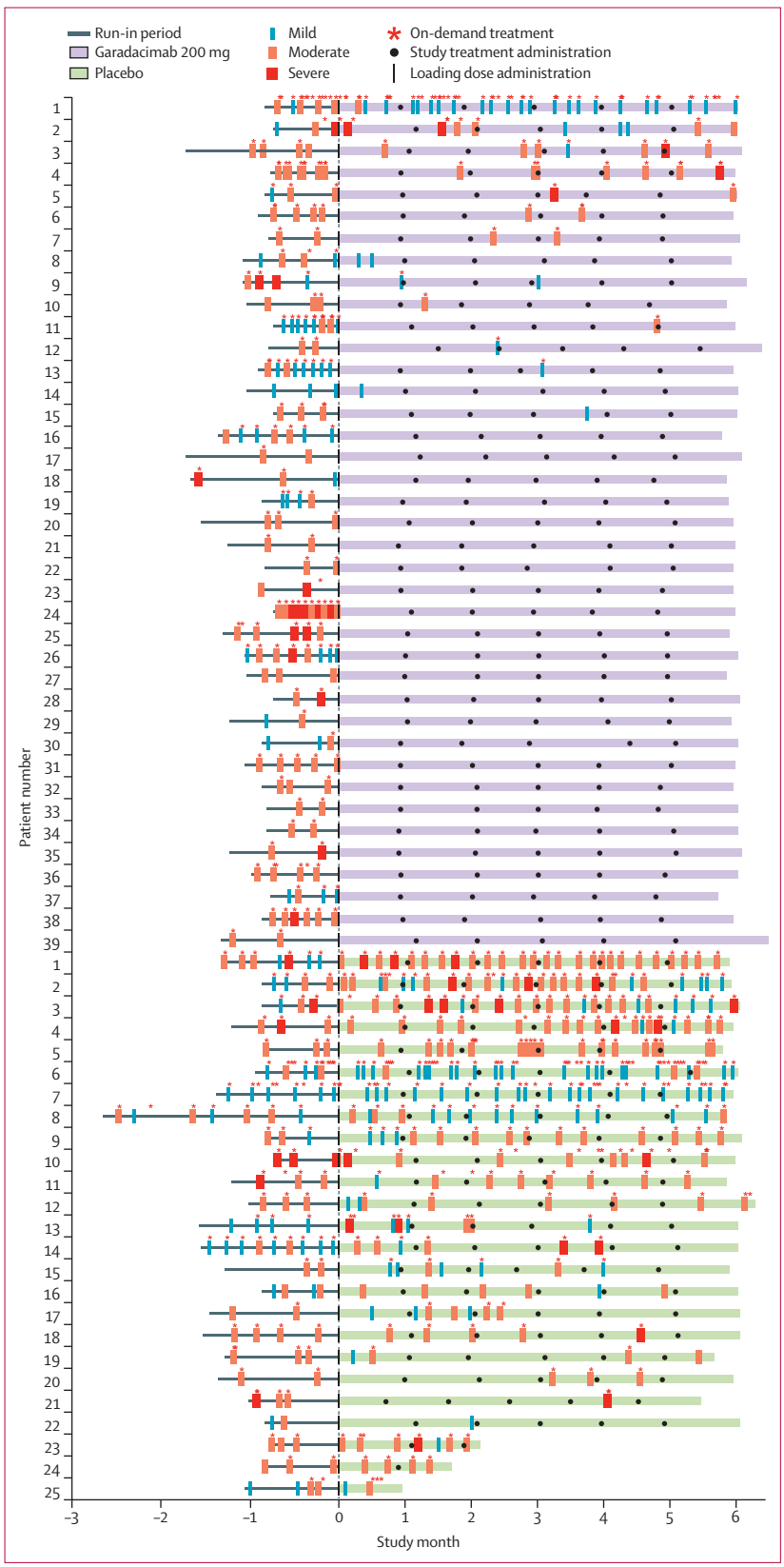


Figure 3: **Percentage reduction in the hereditary angioedema attack rate per month compared with the run-in period**

Fisher exact test, nominal p<0·0001 for a reduction of 100% (attack-free). *One patient in the placebo group with less than 30 days of treatment was excluded from analyses, as prespecified in the clinical trial protocol.



attacks from baseline (figure 3). 36 (92%) and 37 (95%) of 39 patients treated with garadacimab had a reduction in attacks of at least 50% or 70% compared with four (17%) and eight (33%) of 24 evaluable patients in the placebo group, respectively.

Patients in the garadacimab group had a lower mean number of attacks per month that required on-demand treatment compared with patients in the placebo group (0·23, 95% CI 0·02 to 0·45 *vs* 1·86, 1·26 to 2·46; figure 4), corresponding to a mean difference of –88%. Patients in the garadacimab group had a lower mean rate of moderate or severe attacks per month (0·13, 95% CI 0·03 to 0·22) compared with placebo (1·35, 0·86 to 1·84; table 2; figure 4). The most common anatomical locations of hereditary angioedema attacks across both treatment groups were cutaneous (238 [72%] of 329 attacks), including cutaneous extremities (176 [53%] attacks), and abdomen (137 [42%] attacks). Five (13%) of 39 patients in the garadacimab group versus 12 (50%) of 24 patients in the placebo group had at least one attack with a maximum severity of moderate; five (13%) patients in the garadacimab group versus ten (42%) patients in the placebo group had at least one attack with a maximum severity of severe (table 2; figure 4). Maximum hereditary angioedema attack severity was the most severe attack confirmed by an investigator.

During the 6-month treatment period, 75 adverse events occurred in 25 (64%) of 39 patients in the garadacimab group and 54 adverse events occurred in 15 (60%) of 25 patients in the placebo group (table 3). The most common treatment-emergent adverse events were upper-respiratory tract infections, nasopharyngitis, and headaches (table 3). One serious, severe adverse event (laryngeal attack) managed with overnight hospitalisation occurred in the garadacimab group and was assessed by the investigator as unrelated to the investigational product; the patient made a full recovery. No adverse events of special interest (ie, anaphylaxis, thromboembolic, or abnormal bleeding events) occurred during the study period. No deaths or treatment discontinuations occurred because of adverse events. Three injection-site reactions, including injection-site erythema, bruising, or pruritus, occurred in two (5%) of 39 patients in the garadacimab group and three (12%) of 25 patients in the placebo group.

Laboratory analyses revealed increased prothrombin fragment 1+2 in one (3%) of 39 patients in the garadacimab group (table 3; appendix p 16) and in no patients in the placebo group. In the garadacimab group, low-titre anti-garadacimab antibodies were detected in one (3%) patient at day 1 (pre-administration) with no anti-garadacimab

Figure 4: **Hereditary angioedema attacks during the run-in and treatment periods, arranged by treatment group and by patient**
The number and severity of attacks in patients in the placebo and garadacimab groups throughout the run-in and treatment periods are shown. Further details regarding the medical history of patient 1 in the garadacimab group are shown in the appendix (p 6).

	Garadacimab 200 mg group (n=39)	Placebo group (n=25)
Treatment-emergent adverse events	25 (64%)	15 (60%)
Common treatment-emergent adverse events in ≥5% of patients by Preferred Term*		
Upper-respiratory tract infection	4 (10%)	2 (8%)
Nasopharyngitis	3 (8%)	1 (4%)
Headache	3 (8%)	4 (16%)
Treatment-emergent adverse events related to study treatment	4 (10%)	3 (12%)
Serious treatment-emergent adverse events	1 (3%)†	0
Treatment-emergent adverse events of special interest	0	0
Severe hypersensitivity or anaphylaxis	0	0
Thromboembolic events	0	0
Bleeding events	0	0
Treatment-emergent adverse events leading to study discontinuation	0	0
Treatment-emergent adverse events leading to death	0	0
Injection-site reactions‡	2 (5%)	3 (12%)§
Injection-site erythema	1 (3%)	2 (8%)
Injection-site bruising	1 (3%)	0
Injection-site pruritus	1 (3%)	0
Other	0	1 (4%)§
Prothrombin fragment 1+2 increased	1 (3%)	0

Data are number of patients who had events, presented as n (%). *Further details on treatment-emergent adverse events classified by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term are reported in the appendix (p 15). †One severe, serious adverse event (laryngeal attack) was assessed as not related to trial treatment: the patient made a full recovery and was kept under hospital observation overnight. ‡Injection-site reaction is summarised by System Organ Class and Preferred Term forming a virtual System Organ Class of Injection Site Reactions. §One patient in the placebo group had a vaccination-site reaction that was reported as an injection-site reaction.

Table 3: **Summary of adverse events**

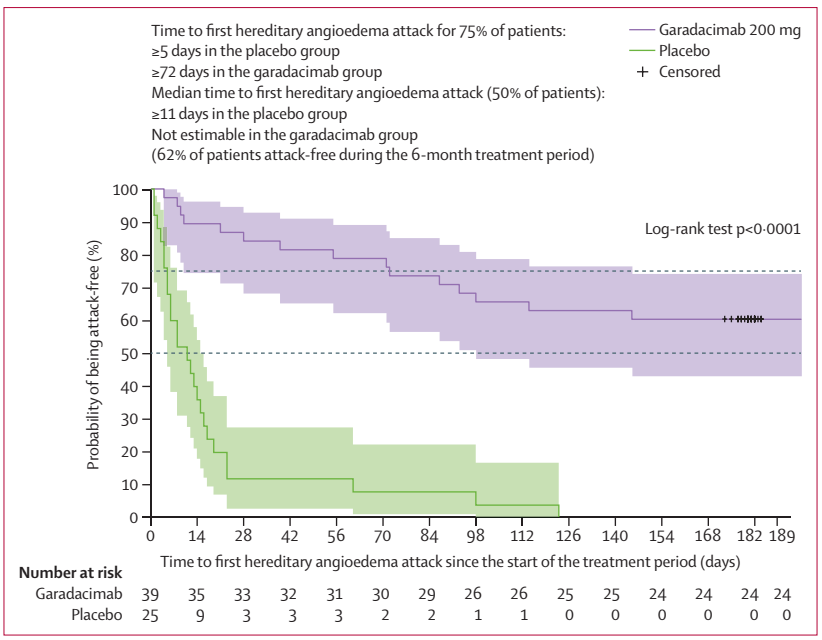


Figure 5: **Time to first hereditary angioedema attack**
Shaded areas represent 95% CIs. Patients with no hereditary angioedema attacks were censored at study visit day 182 or at the end of trial visit (whichever occurred first).

antibodies detected at subsequent visits, and in one (3%) patient at day 182 only (appendix p 17). In the placebo group, no anti-garadacimab antibodies were detected.

From the first dose, 30 (77%) of 39 patients in the garadacimab group had no attacks for at least 72 days compared with at least 5 days for 19 (76%) of 25 patients in the placebo group (figure 5; appendix p 18). The estimated median time to first attack (ie, 50% of patients) for those in the placebo group was 11 days; in the garadacimab group, as more than 50% of patients were attack-free during the 6-month treatment period, the median could not be estimated.

Pharmacokinetic analysis showed that garadacimab concentrations appeared to achieve steady-state exposures after the first (loading) dose and remained consistent over the duration of the monthly treatment period (appendix p 8).

For patients in the garadacimab group, a clinically meaningful improvement (≥6 points)[17] of the mean AE-QoL questionnaire total score at day 31 was observed, with a 23·7-point reduction from the run-in period. Further improvements were observed at day 182, with a 26·5-point reduction. For patients in the placebo group, there was less than a 6-point mean reduction from the run-in period at any timepoint during the 6-month trial (appendix p 9).

Discussion

In this double-blind, randomised, placebo-controlled, phase 3 trial, monthly subcutaneous administrations of the anti-FXIIa monoclonal antibody garadacimab resulted in statistically significant and clinically meaningful reductions in hereditary angioedema attacks compared with placebo. The incidence of adverse events with once-monthly 200 mg garadacimab was similar to that with placebo and there were no reports of thromboembolic events, bleeding, or anaphylaxis. The number of patients reporting injection-site reactions with garadacimab was similar to that with placebo during the 6-month treatment period.

The mojority of patients in the garadacimab group were attack-free during the 6-month treatment period compared with no patients in the placebo group. The beneficial effect of garadacimab was also highlighted by substantial reductions in the mean use of on-demand treatments versus placebo and number of attacks from baseline. In addition to the substantial reduction in the number of attacks per month, garadacimab treatment reduced the number of severe and moderate attacks compared with placebo. Consistent with the improvements in angioedema attack rates and reduction in

severity with garadacimab, SGART results highlighted a favourable assessment of treatment by patients.

Garadacimab showed a favourable safety profile compared with placebo, with a similar incidence of treatment-emergent adverse events across treatment groups. Importantly, in view of the mechanism of action of garadacimab and the physiological role of FXII in coagulation pathways, no patients treated with garadacimab had abnormal bleeding or thromboembolic events. The absence of abnormal bleeding noted in this study is consistent with the absence of an increased bleeding tendency in patients with FXII deficiency.[18] Nevertheless, bleeding and thromboembolic events will be further closely monitored in the open-label extension study. Only one garadacimab-treated patient had low-titre anti-garadacimab antibodies with no clinical sequelae, and no evidence of a reduction in efficacy.

Current hereditary angioedema guidelines indicate that treatments should minimise the number and severity of attacks, reduce angioedema burden and, most importantly, achieve total control of the disease.[1] In view of this goal, the substantial proportion of patients in the garadacimab group who remained attack-free (ie, achieving total control of the disease) with monthly dosing during the 6-month treatment period is a clinically meaningful outcome. Lanadelumab, plasma-derived C1-INH, or berotralstat are recommended as first-line long-term prophylactic therapies for hereditary angioedema.[1] For context, and acknowledging the limitations of cross-trial comparisons, a similarly designed 6-month phase 3 trial showed that prophylactic treatment with 300 mg lanadelumab every 4 (or 2) weeks reduced the least squares mean number of attacks per month by 73% (or 87%) from placebo and led to 31% (or 44%) of patients being attack-free.[19] In the trial presented here, once-monthly 200 mg garadacimab reduced the least squares mean number of attacks per month by 89% compared with placebo and protected 62% of patients from hereditary angioedema attacks throughout the entire 6-month treatment period.

Early onset of protection with garadacimab was evident from the first dose, with almost three-quarters of patients being attack-free within the first 3 months, and efficacy was sustained during the second 3-month period. Considering these data, it is possible that garadacimab might offer protection from hereditary angioedema attacks from the first dose, and that protection against attacks continues throughout the treatment period. Garadacimab-treated patients also had substantial clinically meaningful improvements in quality of life at 31 days from the start of the trial, which was further improved by the end of the 6-month trial period.

The limitations of this trial are the small sample size (albeit typical for a rare disease), the relatively short treatment period of 6 months, and inadequate racial and ethnic representation, all of which have also been reported in other trials.[13,20] Long-term safety and efficacy are being investigated in the open-label extension study.

In conclusion, this phase 3 trial showed the efficacy of prophylactic monthly subcutaneous garadacimab in reducing hereditary angioedema attacks compared with placebo, with a favourable safety profile. Our results support the use of garadacimab as a potential prophylactic therapy for the treatment of hereditary angioedema in adolescents and adults.

Contributors

All authors contributed to data interpretation, review, and approval of the manuscript for publication. HFe, FG, and IJ contributed to study conceptualisation, formal analysis, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, data validation and visualisation, and reviewed and provided input on the manuscript. TJC, AR, HHL, JSJ, JAB, HFa, WHY, ESGS, IO, RTa, MEM, WRL, IMS, EA-P, BR, GLS, JA, KK, YS, PS, RTr, and MM were investigators in the clinical trial. All authors reviewed and edited the manuscript and participated in the decision to submit for publication. TJC, HFe, FG, and IJ accessed and verified the underlying study data. All authors assume responsibility for the completeness and accuracy of the data, the fidelity of the trial and this manuscript, the protocol, and the statistical analysis plan. All authors had full access to all data in the study.

Declaration of interests

TJC is a speaker for Pharming, CSL Behring, Takeda, Fresenius Kabi, and Grifols; has received research and consultancy grants from CSL Behring, Takeda, BioCryst, Ionis, Spark, BioMarin, Fresenius Kabi, and Grifols; and is on the medical advisory board for the US Hereditary Angioedema Association, Director of ACARE Angioedema Center at Penn State University, Hershey, and on the Board of Directors for the American Academy of Allergy, Asthma, and Immunology. AR received research grants as a principal investigator, speaker, and advisor for CSL Behring, Takeda-Shire, BioCryst, Pharming, Pharvaris, Ionis, and Shulov Innovative Science. HHL is a speaker for Pharming, CSL Behring, Takeda, and BioCryst and has received research and consultancy grants from CSL Behring, Takeda, BioCryst, Ionis, BioMarin, Pharming, and Phavaris. JSJ is a speaker for Takeda-Shire, CSL Behring, Teva, AstraZeneca, GSK, Sanofi Genzyme, and Regeneron and has received research funding or consultancy fees from CSL Behring, Takeda-Shire, BioCryst, Novartis, Genentech, AstraZeneca, Allakos, Fresenius Kabi, GSK, and Regeneron. JAB is a consultant, principal investigator, and speaker for CSL Behring, Takeda-Shire, Pharming, and BioCryst; is a consultant or principal investigator for KalVista, Biomarin, and Ionis; and is a consultant for Astria, ONO Pharmaceutical, Pharvaris, and Cycle Pharmaceuticals. HFa received research grants from CSL Behring, Takeda, and Pharming; has served as an advisor for CSL Behring, Takeda, Pharming, KalVista, ONO Pharmaceutical, and BioCryst; and has participated in clinical trials or registries for BioCryst, CSL Behring, Pharming, KalVista, Pharvaris, and Takeda. WHY has been a speaker and advisory board member and has received honoraria from CSL Behring, Takeda-Shire, Novartis, Sanofi Genzyme, and Merck; has received research grants from CSL Behring, Takeda-Shire, BioCryst, Pharming, Aimmune, DBV Technologies, Eli Lilly, Pharvaris, AstraZeneca, Novartis, GSK, Genentech-Roche, Amgen, Sanofi Genzyme, Regeneron, Galderma, AnaptysBio, Glenmark, ALK Pharma, Dermira, Ionis, and Celgene; serves as a medical advisor (volunteer) for HAE Canada, a patient organisation; and is a member of Angioedema Centers of Reference and Excellence. ESGS has received lecturing or advertising board fees from Amgen, Sanofi, Novartis, AstraZeneca, Esperion, Ionis-Akcea, and Merck, paid to their institution. IO has received honoraria or served as a consultant or participated in advisory boards for CSL Behring, Takeda-Shire, and Torii Pharmaceutical Company. RTa is a speaker for BioCryst, CSL Behring, Pharming, AstraZeneca, Sanofi-Regeneron, GSK, and Takeda; has served as a consultant for BioCryst, CSL Behring, KalVista, Pharming, and Takeda; and has received grants or research support from BioCryst, CSL Behring, Ionis, KalVista, Pharvaris, and Takeda. MEM is a speaker for CSL Behring, Takeda, Pharming, BioCryst, GSK, Amgen, Sanofi-Regeneron, AstraZeneca, Blueprint, and Genentech; has received research grants from CSL Behring, Takeda, Pharming, BioCryst, KalVista, Pharvaris,

GSK, Novartis, Merck, and Allakos; and has been a consultant for CSL Behring, Takeda, Pharming, BioCryst, KalVista, and Cycle Pharmaceuticals. WRL is a speaker for CSL Behring, Pharming, AstraZeneca, Sanofi-Regeneron, GSK, and Takeda-Shire; has served as a consultant for BioCryst, BioMarin, CSL Behring, Fresenius Kabi, Intellia, KalVista, Pharming, Pharvaris, and Takeda-Shire; is a board member of the US Hereditary Angioedema Association Medical Advisory Board; and has received grants or research support from ALK Pharma, BioCryst, CSL Behring, Ionis, Gossamer, KalVista, Kedrion, Therapure, and Takeda-Shire. IMS has received honoraria, research funding, and travel grants from BioCryst, CSL Behring, Pharming, Octapharma, KalVista, and Takeda-Shire and has served as a consultant or participated in advisory boards for these companies. EA-P has received honoraria as a speaker or advisor or grant support or clinical trial investigator support from BioCryst, BioMarin Europe, Centogene, CSL Behring, KalVista, Pharming, Pharvaris, and Takeda-Shire. BR has been a speaker and advisory board member for CSL Behring and Takeda, but has not received personal reimbursement for these activities. BR has participated in multiple clinical trials involving investigational drugs for CSL Behring, Takeda, BioCryst, Dyax, and Pharming, but does not hold patents or investments with these companies or involving this product, and serves as a volunteer Medical Scientific Advisor to HAE Canada, a patient organisation. GLS has been an advisory board member for CSL Behring and has participated in clinical trials for investigational drugs for CSL Behring, Takeda, BioCryst, Dyax, Pharming, Pharvaris, and KalVista. JA is a speaker bureau member for CSL Behring, Pharming, BioCryst, and Takeda and has received consulting fees from; is a clinical trial investigator for BioCryst, CSL Behring, Pharming, Takeda, KalVista, Pharvaris, and BioMarin; and has received consulting fees from Cycle Pharmaceuticals. KK has been a clinical trial investigator for CSL Behring. YS has received speaker fees from Novartis, AstraZeneca, Takeda-Shire, and Torii Pharmaceutical Company and has been a clinical trial investigator for CSL Behring. PS has received honoraria, research funding, travel grants, or has served as a consultant or participated in advisory boards for CSL Behring, Octapharma, Pharming, Shire, and Takeda. RTr has received honoraria, travel grants, or has participated in clinical trials or advisory boards for CSL Behring, Shire, and Takeda. HFe, FG, and IJ are full-time employees and shareholders of CSL Behring. MM has received financial support from CSL Behring for acting as a study centre investigator during the conduct of the study and personal fees from CSL Behring, Takeda-Shire, Pharming, BioCryst, Novartis, Octapharma, and KalVista outside the submitted work.

Data sharing

CSL Behring will consider requests to share individual patient data (IPD) from CSL Behring-sponsored studies with external bona-fide, qualified scientific and medical researchers on a case-by-case basis. When appropriate, IPD will generally be shared once review by major regulatory authorities (eg, US Food and Drug Administration or European Medicines Agency) is complete and the primary publication is available. Proposed research should seek to answer a previously unanswered important medical or scientific question. Requests should reflect those important questions. Applicable country-specific privacy and other laws and regulations will be considered and might prevent sharing of IPD. A research proposal detailing the use of the IPD will be reviewed by an internal CSL Behring review committee. If the request is approved, and the researcher agrees to the applicable terms and conditions in a data sharing agreement, IPD that has been appropriately anonymised will be made available. Supporting documents, including the study protocol and statistical analysis plan will also be provided to the researcher. For information on the process and requirements for submitting a voluntary data sharing request for IPD, please contact CSL Behring at clinicaltrials@cslbehring.com.

Acknowledgments

We thank the study investigators, trial site coordinators, and patients who participated in this trial; the independent data monitoring committee members Bruce Zuraw (chairperson), Konrad Bork, and Danny Cohn for their support in the conduct of the study; and Lolis Wieman, John-Philip Lawo, Ingo Pragst, and Mary Scozzafava of CSL Behring for coordinating the trial and providing invaluable assistance in reviewing the manuscript. Medical writing assistance was provided by Anita Toscani (OPEN Health, London, UK) and was funded by CSL Behring.

References

1 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.
2 Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract* 2021; **9:** 132–50.
3 Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992; **71:** 206–15.
4 Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol* 2013; **111:** 329–36.
5 Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis* 2014; **9:** 99.
6 Bork K, Anderson JT, Caballero T, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. *Allergy Asthma Clin Immunol* 2021; **17:** 40.
7 Schmaier AH. The elusive physiologic role of Factor XII. *J Clin Invest* 2008; **118:** 3006–09.
8 Davis AE 3rd. The pathogenesis of hereditary angioedema. *Transfus Apheresis Sci* 2003; **29:** 195–203.
9 Hofman ZL, Relan A, Zeerleder S, Drouet C, Zuraw B, Hack CE. Angioedema attacks in patients with hereditary angioedema: local manifestations of a systemic activation process. *J Allergy Clin Immunol* 2016; **138:** 359–66.
10 Weidmann H, Heikaus L, Long AT, Naudin C, Schlüter H, Renné T. The plasma contact system, a protease cascade at the nexus of inflammation, coagulation and immunity. *Biochim Biophys Acta Mol Cell Res* 2017; **1864:** 2118–27.
11 Fijen LM, Bork K, Cohn DM. Current and prospective targets of pharmacologic treatment of hereditary angioedema types 1 and 2. *Clin Rev Allergy Immunol* 2021; **61:** 66–76.
12 Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med* 2017; **376:** 1131–40.
13 Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. *JAMA* 2018; **320:** 2108–21.
14 Cao H, Biondo M, Lioe H, et al. Antibody-mediated inhibition of FXIIa blocks downstream bradykinin generation. *J Allergy Clin Immunol* 2018; **142:** 1355–58.
15 Craig T, Magerl M, Levy DS, et al. Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2022; **399:** 945–55.
16 Craig T, Zuraw B, Longhurst H, et al. Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks. *J Allergy Clin Immunol Pract* 2019; **7:** 1793–802.
17 Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. The Angioedema Quality of Life Questionnaire (AE-QoL)—assessment of sensitivity to change and minimal clinically important difference. *Allergy* 2016; **71:** 1203–09.
18 Renné T, Schmaier AH, Nickel KF, Blombäck M, Maas C. In vivo roles of factor XII. *Blood* 2012; **120:** 4296–303.
19 Takeda. Summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/takhzyro-epar-product-information_en.pdf (accessed Jan 20, 2023).
20 Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial. *J Allergy Clin Immunol* 2021; **148:** 164–72.