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

Timothy Craig, Markus Magerl, Donald S Levy, Avner Reshef, William R Lumry, Inmaculada Martinez-Saguer, Joshua S Jacobs, William H Yang, Bruce Ritchie, Emel Aygören-Pürsün, Paul K Keith, Paula Busse, Henrike Feuersenger, Dipti Pawaskar, Iris Jacobs, Ingo Pragst, Mittie K Doyle

Summary

Background Hereditary angioedema is associated with dysregulation of the kallikrein–kinin system. Factor XII (FXII) is a key initiator of the kallikrein–kinin system, which produces bradykinin, a central mediator of angioedema. Garadacimab (CSL Behring) is a first-in-class, fully human, immunoglobulin G4 monoclonal antibody targeting activated FXII, intended to prevent attacks in patients with C1-esterase inhibitor-deficient hereditary angioedema (HAE-C1-INH). We aimed to investigate garadacimab as a treatment every 4 weeks for patients with HAE-C1-INH.

Methods In this double-blind, placebo-controlled, phase 2 study, patients with HAE-C1-INH were recruited from 12 research centres in Canada, Germany, Israel, and the USA. Eligible patients were aged 18–65 years and must have had at least four attacks of any severity over a consecutive 2-month period during the 3 months before screening or initiation of previous hereditary angioedema prophylaxis. After a run-in period of 4–8 weeks, patients were randomly assigned (1:1:1:1), using an interactive response technology via block randomisation (block sizes of 1–4), to either placebo or 75 mg, 200 mg, or 600 mg garadacimab. Patients were given an initial intravenous loading dose, and then, on day 6 and every 4 weeks for 12 weeks, they were given a subcutaneous dose of their allocated treatment. The primary endpoint was the number of monthly attacks in the intention-to-treat population (defined as all patients who underwent screening, provided consent, and were assigned to treatment) during the 12-week subcutaneous administration period assessed in the 200 mg and 600 mg garadacimab groups versus placebo. Safety was assessed in all patients who received at least one dose or partial dose of study treatment. This study is registered with ClinicalTrials.gov, NCT03712228.

Findings Between Oct 29, 2018, and Aug 28, 2019, 54 patients were screened, of whom 32 were randomly assigned to either placebo (n=8) or 75 mg (n=9), 200 mg (n=8), or 600 mg (n=7) garadacimab. The median age was 39·5 years (28·0–52·5) and 18 (56%) of 32 patients were female and 14 (34%) were male. The median number of monthly attacks during the 12-week subcutaneous treatment period was 4·6 (IQR 3·1–5·0) with placebo, 0·0 (0·0–0·4) with 75 mg garadacimab, 0·0 (0·0–0·0) with 200 mg garadacimab, and 0·3 (0·0–0·7) with 600 mg garadacimab. Compared with placebo, the rate of attacks was significantly reduced with garadacimab at 200 mg (reduced by 100% [95% CI 98–101]; p=0·0002) and 600 mg (reduced by 93% [54–110]; p=0·0003). No serious adverse events, deaths, or adverse events of special interest (anaphylaxis, thromboembolic events, and bleeding events) were observed.

Interpretation Garadacimab 200 mg and 600 mg every 4 weeks significantly reduced the number of monthly attacks versus placebo and was well tolerated during the study. Garadacimab is an efficacious, subcutaneous prophylaxis in patients with HAE-C1-INH and warrants phase 3 evaluation.

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Allergy, Asthma and Immunology, Department of Medicine and Pediatrics, Penn State University, Hershey, PA, USA (Prof T Craig DO); **Institute of Allergology, Charité-Universitätsmedizin Berlin, Berlin, Germany** (Prof M Magerl MD); **Division of Allergy and Immunology, University of California, Irvine, CA, USA** (Prof D S Levy MD); **Allergy, Immunology and Angioedema Center, Barzilai University Hospital, Ashkelon, Israel** (A Reshef MD); **AARA Research Center, Dallas, TX, USA** (Prof W R Lumry MD); **HZRM Haemophilia Center Rhein Main, Mörfelden-Walldorf, Germany** (I Martinez-Saguer MD); **Allergy and Asthma Clinical Research, Walnut Creek, CA, USA** (J S Jacobs MD); **Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, ON, Canada** (W H Yang MD); **Division of Hematology, Department of Medicine, University of Alberta, Edmonton, AB, Canada** (Prof B Ritchie MD); **Department of Children and Adolescents, University Hospital Frankfurt, Goethe University, Frankfurt, Germany** (E Aygören-Pürsün MD); **McMaster University Medical Centre Site, Hamilton, ON, Canada** (Prof P K Keith MD); **Division of Clinical Immunology and Allergy, Department of Medicine, Icahn School of Medicine at**

Introduction

Hereditary angioedema is a rare and potentially life-threatening autosomal dominant disease characterised by recurrent and unpredictable attacks of angioedema in the skin, genitals, intestinal wall, and upper airways.[1–4] Factor XII (FXII) is a key initiator of the intrinsic contact activation system and the kallikrein–kinin pathway. FXII also participates in the initiation of the fibrinolytic and complement pathways.[5–7] Activation of FXII leads to the production of bradykinin, a central mediator of angioedema downstream of the kallikrein–kinin pathway.[5,8,9] In healthy individuals, C1-esterase inhibitor (C1-INH), a key inhibitor of numerous serine proteases, regulates the kallikrein–kinin pathway.[9] However, in patients with hereditary angioedema who have a deficiency of C1-INH (ie, patients who have HAE-C1-INH),[2] the kallikrein–kinin pathway is unregulated and bradykinin is overproduced, causing

Mount Sinai, New York, NY, USA (P Busse MD)**; CSL Behring Innovation GmbH, Marburg, Germany** (H Feuersenger PhD, I Pragst PhD)**; CSL Behring, King of Prussia, PA, USA** (D Pawaskar PhD, I Jacobs MD, M K Doyle MD)**; Janssen Research & Development LLC, Spring House, PA, USA** (D Pawaskar)**; Aro Biotherapeutics, Philadelphia, PA, USA** (M K Doyle)

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

Research in context

Evidence before this study

Despite the remarkable progress in the management of hereditary angioedema, patients still face a substantial disease burden that restricts their daily life, both physically and mentally, due to the unpredictability of attacks. Several therapies are currently licensed for the treatment of patients with hereditary angioedema, but few have been proven to be efficacious and well tolerated for long-term prophylaxis. Improvement on current therapies to further reduce the frequency of attacks while maintaining convenient dosing is a desirable treatment goal and is expected to make a vast improvement in the disease course of patients with this life-long genetic disorder. We searched the MEDLINE database using the terms "hereditary angioedema" AND "prophylaxis" and then filtered the search results to select articles describing randomised controlled trials that were published between Jan 1, 2018, and Feb 12, 2021. Only nine randomised controlled trials were published during this period. Of these, six were trials involving C1-esterase inhibitor (C1-INH) concentrates and the other three were trials investigating the kallikrein inhibitors: avoralstat, berotralstat, and lanadelumab. To date, no studies have reported on the prophylaxis of hereditary angioedema by targeting the initiator of the kallikrein–kinin pathway, activated factor XII (FXIIa).

Added value of this study

This phase 2, double-blind, placebo-controlled, randomised study provides the first clinical evidence for the role of FXIIa in hereditary angioedema. Additionally, we found that subcutaneous administration of either 200 mg or 600 mg garadacimab every 4 weeks for a total of 12 weeks significantly reduced the number of monthly attacks by over 90% in patients with HAE-C1-INH compared with placebo (p<0·001).

Implications of all the available evidence

Garadacimab, a first-in-class recombinant monoclonal antibody targeting FXIIa, was efficacious and well tolerated when subcutaneously administered every 4 weeks. Furthermore, a phase 3 study is warranted to establish the value of garadacimab for prophylactic use in patients with hereditary angioedema who have a deficiency of C1-INH.

See Online for appendix

increased vascular permeability and subsequent angioedema.[4,5,9]

Patients with hereditary angioedema face a substantial disease burden, and approximately 50% of patients will experience at least one potentially fatal laryngeal attack during their lifetime.[2,10,11] The impact of these attacks affects patients both physically, by the restriction of daily activities, and mentally, because of the unpredictability of attacks and the potential for them to be life-threatening.[4,12–15] A prophylactic treatment that can be given regularly for the prevention of attacks could reduce the disease burden on patients with hereditary angioedema, their families, and the healthcare system.

Garadacimab (CSL312) is a first-in-class, fully human, immunoglobulin G4 monoclonal antibody targeting activated FXII (FXIIa).[16] Garadacimab has picomolar affinity for FXIIa and has been shown to prevent bradykinin formation in plasma samples from patients with hereditary angioedema.[16] Garadacimab, unlike other treatments for hereditary angioedema,[17,18] inhibits the kallikrein–kinin pathway initiator, FXIIa,[16] thereby decreasing downstream bradykinin production.

We aimed to assess the efficacy and safety of garadacimab in the prevention of attacks in patients with HAE-C1-INH.

Methods

Study design and participants

This randomised, double-blind, placebo-controlled, phase 2 study investigated the efficacy and safety of garadacimab in patients with hereditary angioedema. The full study included patients with HAE-C1-INH or hereditary angioedema with normal levels of C1-INH, and either a FXII or plasminogen mutation (appendix p 8). Here, we report on analyses including only patients with HAE-C1-INH enrolled in the randomised, blinded, placebo-controlled period.

Patients were recruited from 12 research centres across four countries (Canada, Germany, Israel, and the USA). Potentially eligible patients entered a run-in period of 4–8 weeks to assess their underlying disease status (eg, frequency of attacks) and their eligibility for the study.

Patients were eligible if they were aged 18–65 years with a diagnosis of HAE-C1-INH based on the following criteria: documented clinical history consistent with hereditary angioedema, C1-INH functional activity of less than 50% of the lower limit of the reference range (70–130% of normal plasma[19]), and a C4 antigen concentration below the lower limit of the reference range (0·16–0·38 mg/mL[19]). Additionally, patients must have had at least four attacks of any severity over a consecutive 2 month period during the 3 months before screening or initiation of previous hereditary angioedema prophylaxis, and be willing to stop using C1-INH therapy, androgens, or antifibrinolytics for routine prophylaxis of attacks on the first day of the run-in period (allowing for a wash-out period of ≥4 weeks). Once screened, patients were permitted to use an acute rescue medication of their choice to manage attacks of any severity and location.

Patients were excluded if there was presence or history of clinically significant arterial or venous thrombosis, or significant prothrombotic risk (as determined by the investigator), or current or history of uncontrolled abnormal bleeding events or risk of bleeding events. Further exclusion criteria are in the appendix (p 2).

Patients were recruited by the study investigators and all patients provided written informed consent before enrolment. Ethics approval was obtained from either site-level or country-level institutional review boards or ethics committees (appendix p 3). This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines. A copy of the redacted protocol is in the appendix (pp 12–138).

Randomisation and masking

Patients who met all eligibility criteria after the run-in period were randomly assigned (1:1:1:1), using an interactive response technology and block randomisation (block sizes of 1–4), to either placebo or 75 mg, 200 mg, or 600 mg garadacimab. Subsequent to randomisation of the first 32 enrolled participants, six additional patients were assigned to receive open-label treatment with garadacimab once every 2 weeks. The randomisation list was kept within the interactive response technology during the study, and site staff and CSL Behring representatives did not have access. All patients and investigational site staff were masked to treatment assignment. In an emergency situation, the randomisation code for patients could be revealed to a site using the interactive response technology during the study. Representatives from CSL Behring (or their delegates) with direct interaction with the study sites or patients were masked to treatment assignment. To maintain masking, all doses of garadacimab and placebo administered were volume-normalised in an opaque or coloured syringe. Personnel analysing the data were unmasked to treatment assignment and instructed to keep the randomisation assignment confidential.

Procedures

Initial intravenous loading doses of placebo and 40 mg, 100 mg, and 300 mg garadacimab (CSL Behring, Parkville, VIC, Australia) were administered on day 1, followed by subcutaneous treatment with placebo and 75 mg, 200 mg, and 600 mg garadacimab, respectively, depending on group assignment, on day 6 and every 4 weeks thereafter for 12 weeks (ie, on week 5, day 35, and on week 9, day 63); referred to as the 12-week subcutaneous administration period throughout (appendix p 4).

Patients were given access to an electronic diary (eDiary) to record the occurrence of any attack or adverse event. Full details of the information captured in the eDiary are listed in the appendix (p 2).

During the run-in period, patients were contacted by telephone every 2 weeks from week 1 to review eDiary data (documenting any attacks or adverse events), confirm access to rescue medication, and discuss any concomitant medication. During the treatment period, follow-up visits at the study site occurred every 2 weeks from day 1. During the day 1 visit, eligibility to enter the treatment period was confirmed. Further assessments on day 1 included a physical examination, measurement of vital signs, urinalysis, administration of placebo or garadacimab, blood draws (before-dose blood draw was to be analysed for haematology, biochemistry, and coagulation parameters [eg, activated partial thromboplastin time], viral serology, and immunogenicity; blood draws at 0·5, 4·0, and 8·0 h after dose were to be analysed for pharmacodynamics), pregnancy testing, confirming access to rescue medication, review of eDiary (document any attacks or adverse events), and review of concomitant medication. Similar assessments were done at each visit to study centre to receive study drug (ie, on day 6 and every 4 weeks thereafter for 12 weeks). A detailed table of timings of assessments is in the appendix (p 4).

Investigators documented the occurrence of attacks on the basis of the patient's eDiary, the patient's relevant medical history, and their judgment as a physician. Guidance was provided to the investigator to define attack severity. Mild attacks were defined as having little-to-no effect on the patient's ability to perform daily activities and might not have necessarily required rescue medication but might have required treatment with other concomitant medications (eg, analgesics). Moderate attacks were defined as having caused difficulty in performing daily activities or might have required assistance to perform these activities and the use of rescue medication was probable. Severe attacks were defined as having caused substantial limitations in the patient's ability to perform daily activities, might have required medical assistance, and required the use of rescue medication. The investigator was able to ask clarifying questions to assist in their assessment of whether an attack occurred and its severity.

We measured the exploratory biomarker activated factor XII (FXIIa)-mediated kallikrein activity using a chromogenic substrate (S-2302, Chromogenix) with an in-house enzymatic assay method involving ex-vivo activation of the contact system in the plasma samples. We screened for anti-drug antibodies to garadacimab using electrochemiluminescence detection of complexes formed by anti-drug antibodies with biotin- and Sulfo-TagTM-labelled garadacimab after acid dissociation of the samples.

An adverse event was defined as any untoward event that happened to the patient during the course of the study. Adverse events were reported for any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of garadacimab or placebo, whether or not assessed as related. All adverse events were classified using the Medical Dictionary for Regulatory Activities (version 22.0). Adverse events of special interest were thromboembolic events, bleeding events, and anaphylaxis. Adverse events with a start date and time on or after the first injection date and time of investigational product were considered to be treatment-emergent

adverse events. All adverse events were assessed by the investigator as either related or not related to investigational product. All patients entered an extension period of at least 44 weeks and were followed-up for a further 14 weeks (appendix p 8).

Outcomes

The primary endpoint was the time-normalised number of attacks per month experienced by patients in the 200 mg and 600 mg garadacimab groups during the 12-week subcutaneous administration period compared with placebo.

Secondary endpoints were the proportion of patients who responded to garadacimab or placebo (defined as ≥50% relative reduction in number of attacks per month compared with during the run-in period); the proportion of patients who did not have any attacks during the administration period; the proportion of mild, moderate, or severe attacks; the number of attacks (in general and by severity) and the proportion of patients who required rescue medication; the pharmacokinetics of garadacimab (full data to be presented elsewhere); and the safety profile of garadacimab. All secondary endpoints were assessed during the 12-week subcutaneous administration period. The safety of garadacimab was assessed from the time of intravenous loading dose administration; however, here we focus on safety data for the 12-week subcutaneous administration period. Safety assessments analysed during the 12-week subcutaneous administration period included adverse events, serious adverse events, adverse events of special interest (ie, anaphylaxis, thromboembolic events, and bleeding events), injection site reactions, clinically meaningful (as determined by the investigator) abnormalities in laboratory assessments, vital signs, and inhibitory antibodies to garadacimab.

Exploratory endpoints were the number of days per month that patients experienced attacks, the number of rescue medication uses per month, pharmacodynamic biomarkers (eg, FXII concentration, FXIIa-mediated kallikrein activity, cleaved high molecular weight kallikrein, C1-INH antigen concentration, C1-INH functional activity, C4 antigen concentration, activated partial thromboplastin time, and D-dimer concentration), and investigator-reported and patient-reported outcomes (Angioedema Quality of Life, Work Productivity and Activity Impairment, Subject's Global Assessment of Response to Therapy, Investigator's Global Assessment of Response to Therapy). and FXIIa-mediated kallikrein activity). Here, we report the pharmacodynamic markers of activated partial thromboplastin time and FXII-mediated kallikrein activity; all other exploratory endpoints will be reported elsewhere. The baseline for pharmacokinetic and pharmacodynamic analyses was defined as week 1, day 1, before the intravenous loading dose.

Statistical analysis

We determined that seven patients were needed in each group to reach a power of approximately 82% for the

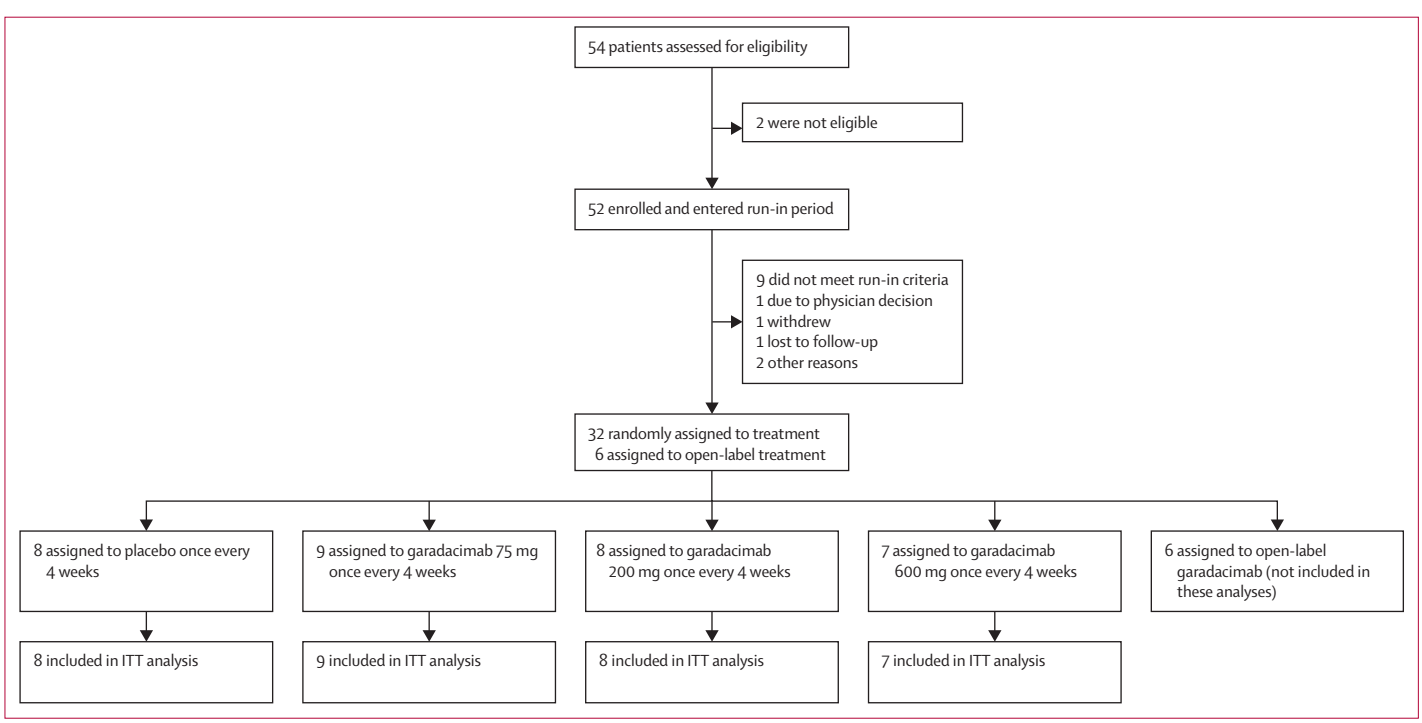

Figure 1: **Trial profile**
ITT=intention-to-treat.

comparisons of 200 mg garadacimab versus placebo and 600 mg garadacimab versus placebo using two-sided Mann–Whitney *U* tests. To account for multiple testing, we evenly split the α level of 5% between the hypotheses tested. Therefore, the 200 mg or 600 mg garadacimab doses were each tested against placebo for a difference in the attack rate at an α level of 0·025. We tested the 75 mg garadacimab dose against placebo for the median number of monthly attacks in a post-hoc analysis.

We analysed demographic patient characteristics and primary endpoint data in the intention-to-treat (ITT) population (defined as all patients who provided informed consent, underwent study screening procedures, and were assigned to treatment). The safety population comprised all patients who provided informed consent, were assigned to treatment, and received at least one dose or partial dose of garadacimab or placebo. Secondary and exploratory endpoints were assessed in the ITT population. Pharmacodynamic data were analysed using the pharmacodynamic population, which comprised all patients in the safety population for whom at least one pharmacodynamic measurement was recorded.

We present continuous variables using mean values with their respective 95% CI or SD, median (IQR), and counts of missing and non-missing values. We present categorical values using counts and percentages.

We calculated the number of monthly attacks by dividing the number of attacks of each patient by the length of the patient's assessment period in days, multiplied by 30·4375. There were no missing data for the number of monthly attacks; therefore, no imputation of missing data was needed or performed.

In a planned post-hoc analysis, we did pharmacokinetic and pharmacodynamic modelling in a population-based exposure–response analysis to further investigate our FXIIa-mediated kallikrein activity results.

We did all analyses using SAS (version 9.3 or later). We considered p values of 0·05 or less to be significant. An independent data and safety monitoring board regularly monitored trial safety and provided recommendations to the sponsor on safety-related trial conduct. This trial is registered at ClinicalTrials.gov, NCT03712228.

Role of the funding source

The study was designed by the sponsor (CSL Behring), in collaboration with key investigators (TC, MM, DSL, AR, WRL, IM-S, JSJ, WHY, BR, EA-P, and PB). Employees of the sponsor who are named authors (IJ, IP, MKD, and DP) had a role in data collection, data analysis, and data interpretation. The sponsor reviewed the data from the study and the final manuscript before submission.

Results

Between Oct 29, 2018, and Aug 28, 2019, 54 patients with HAE-C1-INH were screened and 52 patients were entered into the run-in period. 32 eligible patients were randomly assigned to placebo (n=8), 75 mg (n=9), 200 mg (n=8), or 600 mg garadacimab (n=7) after the run-in period (figure 1; ITT population). The median age was 39·5 years (IQR 28·0–52·5) and 18 (56%) of 32 patients were female and 14 (34%) were male (table 1). 30 (94%) of 32 patients were diagnosed with type 1 HAE-C1-INH and two (6%) had type 2 HAE-C1-INH.

On the basis of 2 consecutive months in a 3-month period, the median number of monthly attacks before screening or initiation of previous hereditary angioedema prophylaxis was 4·3 (IQR 2·8–5·3) in the placebo group, 7·5 (5·5–9·0) in the 75 mg garadacimab group, 4·0 (3·0–5·5) in the 200 mg garadacimab group, and 3·5 (2·0–4·0) in the 600 mg garadacimab group. The median number of monthly attacks during the run-in period was 4·6 (IQR 3·2–7·3) in the placebo group, 6·3

	Placebo group (n=8)	75 mg garadacimab group (n=9)	200 mg garadacimab group (n=8)	600 mg garadacimab group (n=7)
Age, years	39·5 (33·5–53·5)	46·0 (43·0–55·0)	38·5 (30·5–49·0)	24·0 (23·0–29·0)
Sex				
Female	4 (50%)	7 (78%)	2 (25%)	5 (71%)
Male	4 (50%)	2 (22%)	6 (75%)	2 (29%)
Race				
White	7 (88%)	9 (100%)	8 (100%)	5 (71%)
Asian	0	0	0	2 (29%)
Black or African American	0	0	0	0
Other*	1 (13%)	0	0	0
Country of recruitment				
Canada	1 (13%)	2 (22%)	2 (25%)	1 (14%)
Germany	3 (38%)	3 (33%)	4 (50%)	3 (43%)
Israel	0	2 (22%)	2 (25%)	1 (14%)
USA	4 (50%)	2 (22%)	0	2 (29%)
Body-mass index, kg/m²	28·6 (26·0–30·8)	28·0 (20·7–31·6)	29·68 (26·7–31·9)	25·94 (20·9–29·4)
HAE-C1-INH type				
Type 1	7 (88%)	9 (100%)	7 (88%)	7 (100%)
Type 2	1 (13%)	0	1 (13%)	0
Hereditary angioedema prophylaxis during the 3 months before screening				
Yes	1 (13%)	6 (67%)	1 (13%)	3 (43%)
No	7 (88%)	3 (33%)	7 (88%)	4 (57%)
Previous exposure to hereditary angioedema prophylaxis				
C1-INH (intravenous)	4 (50%)	9 (100%)	7 (88%)	5 (71%)
Icatibant	4 (50%)	2 (22%)	4 (50%)	5 (71%)
Conestat alfa	1 (13%)	0	1 (13%)	0
C1-INH (subcutaneous)	1 (13%)	1 (11%)	1 (13%)	0
Number of attacks per month during run-in period				
Median	4·6 (3·2–7·3)	6·3 (5·1–7·6)	5·7 (2·8–6·5)	3·0 (2·8–4·8)
Mean	5·1 (2·4)	6·1 (1·8)	5·7 (3·7)	3·5 (1·5)

Data are n (%), mean (SD), or median (IQR). Garadacimab and placebo were administered every 4 weeks. Proportions might not add up to 100% due to rounding. C1-INH=C1-esterase inhibitor. HAE-C1-INH=hereditary angioedema due to deficient C1-esterase inhibitor *Includes Mixed race, American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander.

Table 1: **Baseline characteristics, intention-to-treat population**

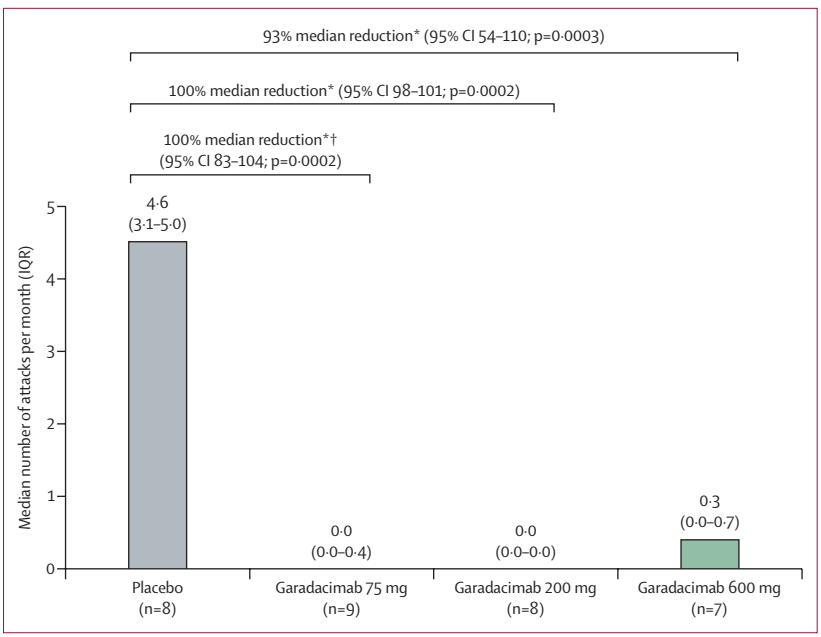

Figure 2: **Median number of monthly attacks during the randomised period (12 weeks)**
*Median reduction in the number of attacks compared with placebo. †The 75 mg garadacimab dose was assessed against placebo in a post-hoc analysis.

(5·1–7·6) in the 75 mg garadacimab group, 5·7 (2·8–6·5) in the 200 mg garadacimab group, and 3·0 (2·8–4·8) in the 600 mg garadacimab group. For all garadacimab groups combined, the median number of monthly attacks during the run-in period was 5·2 (IQR 3·0–6·6).

The median number of monthly attacks during the 12-week subcutaneous treatment period was 4·6 (IQR 3·1–5·0) with placebo, 0·0 (0·0–0·4) with 75 mg garadacimab, 0·0 (0·0–0·0) for 200 mg garadacimab, and 0·3 (0·0–0·7) for 600 mg garadacimab. Furthermore, compared with placebo, 200 mg garadacimab reduced the median attack rate by 100% (95% CI 98–101) and 600 mg garadacimab reduced the median attack rate by 93% (54–110), and patients receiving 200 mg and 600 mg garadacimab had significant reductions in median attack rate compared with those receiving placebo (p=0·0002 for 200 mg and p=0·0003 for 600 mg garadacimab; figure 2). The mean number of monthly attacks during the 12-week subcutaneous treatment period was 4·2 (SD 1·8) with placebo, 0·5 (1·1) with 75 mg garadacimab, 0·1 (0·1) with 200 mg garadacimab, and 0·4 (0·5) with 600 mg garadacimab. In a post-hoc analysis, we found that the 75 mg garadacimab dose reduced the median number of attacks by 100% (95% CI 83–104), a significant reduction, compared with placebo (p=0·0002).

During the 12-week subcutaneous period, all patients who received garadacimab had notable reductions in attack rate compared with those who received placebo, with large proportions of patients having a more than 50% reduction in the rate of attacks required to qualify as a responder (figure 3).

All eight patients (100%) treated with 200 mg garadacimab had a reduction in the number of monthly attacks of at least 90% and seven (88%) were attack free (figure 3). In the 75 mg garadacimab group, eight (89%) of nine patients had a reduction in the number of monthly attacks of at least 90% and five (56%) were attack free. And, for patients treated with 600 mg garadacimab, four (57%) of seven patients had a reduction in the number of monthly attacks of at least 90% and three (43%) were attack free. Of the four patients in the 600 mg garadacimab group who had attacks, three (75%) had a mean of less than 1 attack per month. None of the patients who received placebo had a reduction in the number of monthly attacks of 50% or higher nor were any attack free.

During the 12-week subcutaneous period, 21 attacks occurred across the all garadacimab groups, of which only one was severe (in the 600 mg garadacimab group), and the rest were mild or moderate (figure 4). The severe attack was localised to the abdomen, lasted 3 days, and resolved 8 h after a single dose of rescue medication. No patients in the study had laryngeal attacks. In the placebo group, 20 (21%) of 95 attacks were severe (investigator assessed).

Rescue medication use was assessed in terms of the number of patients and attacks treated. The most commonly used medications were intravenous C1-INH and subcutaneous icatibant and conestat alfa was also used. All eight patients in the placebo group were treated with rescue medication for at least one attack (figure 4). By contrast, three (33%) of nine patients in the 75 mg garadacimab group, one (13%) of eight in the 200 mg garadacimab group, and two (29%) of seven in the 600 mg garadacimab group required rescue medication for at least one attack during the 12-week subcutaneous period. 89 (94%) of 95 attacks in the placebo group, 11 (92%) of 12 attacks in the 75 mg garadacimab group, one (100%) of one attack in the 200 mg garadacimab group, and three (38%) of eight attacks in the 600 mg garadacimab group were treated with rescue medication. Of the 15 attacks treated in the garadacimab groups, all resolved with a single dose of rescue medication. Of the 89 attacks treated in the placebo group, 77 (87%) were treated with one dose of rescue medication, six (7%) with two doses, three (3%) with three doses, two (2%) with four doses, and one (1%) with seven doses.

Although the safety data presented here focus on the 12-week subcutaneous treatment period, adverse events observed after the initial loading dose on day 1 and before subcutaneous administration on day 6 are in the appendix (p 5).

In the garadacimab groups, 53 treatment-emergent adverse events were reported in the 12-week subcutaneous treatment period and all were determined to be mild (35 events that occurred in 15 [63%] of 24 patients) or moderate (18 events that occurred in 11 [46%]). Most treatment-emergent adverse events were

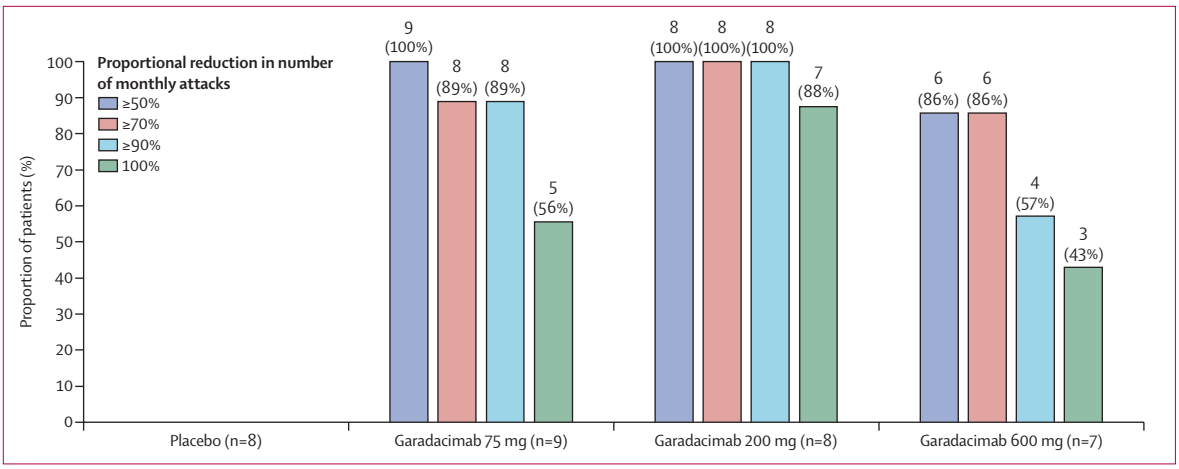

Figure 3: **Proportional reduction in the number of monthly attacks compared with during run-in period**

resolved (51 events in 20 [83%] of 24 patients) or considered to be resolving (one event in one [4%] patient) during garadacimab treatment. The proportion of patients who had at least one treatment-emergent adverse event with garadacimab was similar to that of patients in the placebo group (20 [83%] of 24 patients in the garadacimab groups and six [75%] of eight patients in the placebo group). There were no serious treatment-emergent adverse events, adverse events of special interest (anaphylaxis, thromboembolic events, or bleeding events), or adverse events leading to study discontinuation (table 2; appendix pp 6–7).

41 (77%) of 53 treatment-emergent adverse events were assessed by the investigator to be unrelated to treatment. During the 12-week subcutaneous treatment period, the most common treatment-emergent adverse events associated with administration were injection site reactions, which occurred in two (25%) of eight patients in the placebo group, one (11%) of nine in the 75 mg garadacimab group, one (13%) of eight in the 200 mg garadacimab group, and four (57%) of seven in the 600 mg garadacimab group. No treatment-emergent adverse events led to study discontinuation. All adverse events that were assessed to be related to the investigational product resolved over time, without the use of concomitant medication. We found no evidence of anti-drug antibodies in patients treated with garadacimab.

Overall, in the garadacimab groups, inhibition of FXIIa-mediated kallikrein activity was observed (appendix 9). Generally, median FXIIa-mediated kallikrein activity was inhibited in a dose-dependent manner. Overall, activity did not fully return to baseline (pre-dose levels) even after 28 days after the last dose.

At week 13, day 91 (28 days after the final dose of garadacimab or placebo), the median change from baseline in activated partial thromboplastin time was –0·60 s (IQR –1·3 to 1·5) in the placebo group, –1·8 s (02·5 to 0·1) in the 75 mg garadacimab group, –0·9 s (–2·2 to 2·7) in the 200 mg garadacimab group, and 14·1 s (5·4 to 29·3) in the 600 mg garadacimab group.

In a planned post-hoc analysis modelling the pharmacokinetics and pharmacodynamics of FXIIa-mediated kallikrein activity, we found that increasing concentrations of garadacimab seemed to decrease the relative risk of an attack, and that there is no additional efficacy benefit with 600 mg garadacimab compared with 75 mg or 200 mg (appendix p 10).

Discussion

We found that subcutaneous administration of either 200 mg or 600 mg garadacimab, an FXIIa-targeted monoclonal antibody, every 4 weeks over a period of 12 weeks significantly reduced the median number of monthly attacks by over 90% compared with placebo in patients with HAE-C1-INH. Additionally, 88% of patients treated with 200 mg garadacimab were attack free after 12 weeks of treatment and fewer patients in the 75 mg, 200 mg, and 600 mg garadacimab groups required rescue medication than did those in the placebo group. Thus, garadacimab might substantially reduce patients' need for further medical intervention and allow many patients to live attack free.

In exploratory analyses, we found that all doses of garadacimab inhibited FXIIa-mediated kallikrein activity in ex-vivo assays to some degree, suggesting that garadacimab inhibits FXIIa. We assessed the time course of FXIIa-mediated kallikrein activity and found dose-dependent inhibition, highlighting that even partial inhibition might be sufficient for garadacimab efficacy. This observation supports phase 1 data that showed concentration-dependent inhibition of FXIIa-mediated kallikrein activity after single increasing doses of intravenous and subcutaneous garadacimab.[20] Although the dose-dependent FXIIa-mediated kallikrein activity did not appear to correlate with the observed reduction in the number of monthly attacks, post-hoc modelling of pharmacokinetics and pharmacodynamics suggested

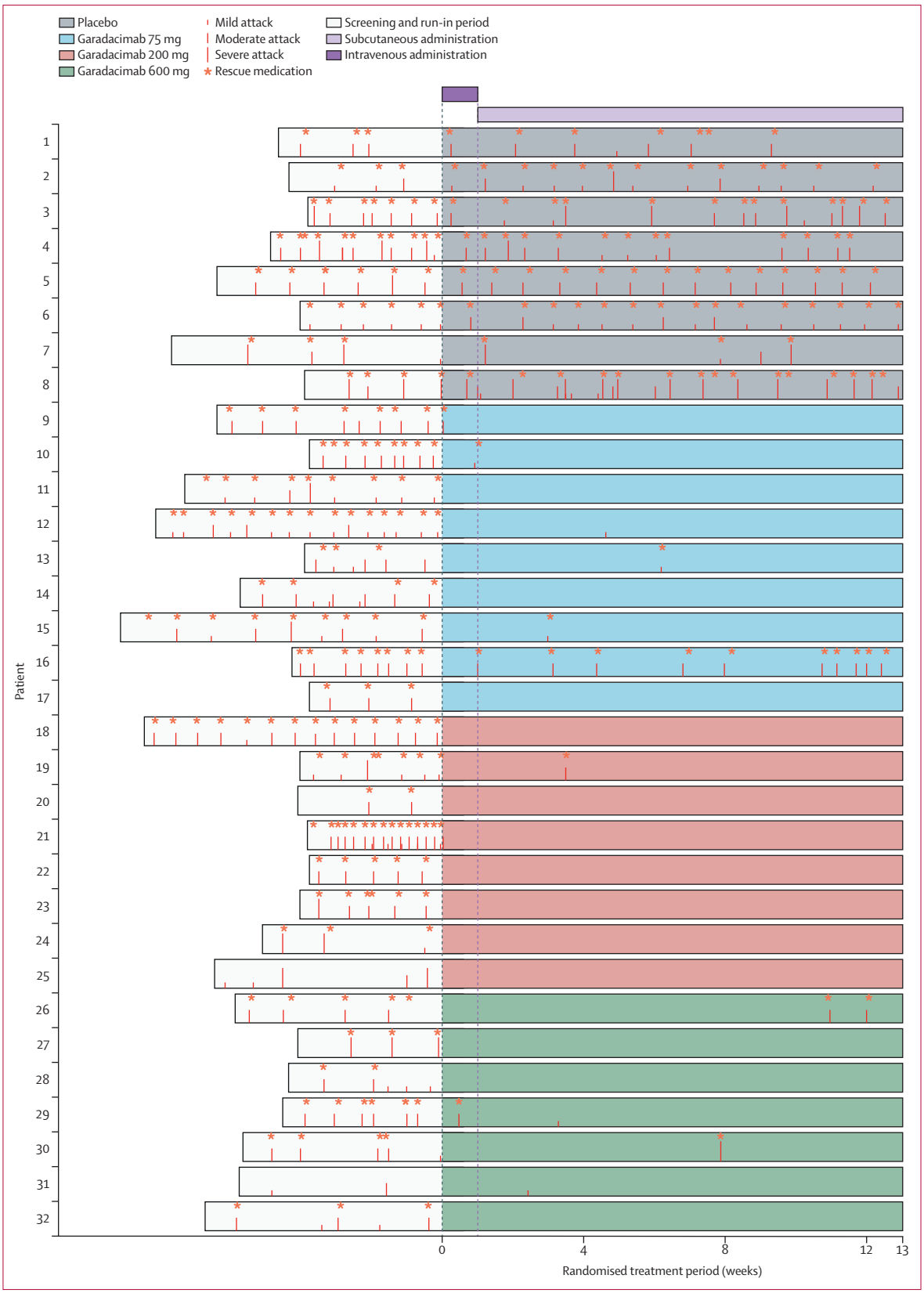

Figure 4: **Number and severity of attacks and use of rescue medication per patient (intention-to-treat population)**
This figure highlights the number and severity of attacks experienced by patients in the placebo and garadacimab groups throughout the screening and run-in period and 13 weeks of treatment (1 week of intravenous and 12 weeks of subcutaneous administration).

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that increasing concentrations of garadacimab decreases the relative risk of an attack. Because the assay we used to determine FXIIa-mediated kallikrein activity is an ex-vivo technique, it might not reflect the true inhibition levels observed in vivo. However, the pharmacokinetic and pharmacodynamic correlation suggests that the FXIIa-mediated kallikrein activity assay might be an indicator of the pharmacological effect of garadacimab. Additionally, the initial loading dose resulted in rapid achievement of the steady-state exposure level and the inhibition of FXIIa-mediated kallikrein activity leading to immediate onset of action—a key goal for successful treatment. However, these analyses were exploratory and post hoc, and so adequately powered studies to specifically investigate these interactions will be needed to confirm these findings.

In exploratory analyses of activated partial thromboplastin time, data collected at week 13 (28 days after the third dose of garadacimab or placebo) showed that only the 600 mg garadacimab dose caused a prolongation in activated partial thromboplastin time outside of the normal range (24·3–43·4 s). We did not observe any clinically significant bleeding events, which is in line with the phase 1 data that reported prolongation outside of the normal range in volunteers who were given 10 mg/kg of garadacimab or more, which was found to inhibit FXIIa-mediated kallikrein activity by 85% or more.[20] Therefore, although measurements for activated partial thromboplastin time were not collected between doses, prolongation outside of the normal range would not be expected with 200 mg garadacimab.

Across all treatment groups, no serious adverse events or adverse events of special interest (ie, anaphylaxis, thromboembolic events, or bleeding) were observed, showing that subcutaneous treatment with garadacimab was well tolerated for up to 12 weeks. The absence of haemostatic or prothrombotic effect observed in this study, coupled with reports that patients with FXII deficiency do not experience clinical consequences with regards to bleeding or prothrombotic events, supports the observation that FXII has a small role in fibrinolytic or coagulation pathways.[21,22]

In this phase 2 study, the number of monthly attacks observed in the placebo group during the run-in and assessment periods remained consistent between the two periods, which suggests that any differences seen in the garadacimab groups between the two periods are related to garadacimab, lending further confidence to the observed results. Moreover, the baseline median number of monthly attacks across all garadaci-mab groups in this study (5·2 attacks) was high, highlighting that although garadacimab was investigated in a patient population that might have a high propensity for attacks, efficacious results were still observed. Furthermore, garadacimab has been shown to have a long half-life (18–20 days; unpublished data), which is one reason why garadacimab might be expected to confer extended protection for patients with hereditary angioedema, allowing it to be administered every 4 weeks. This hypothesis is supported by the absence of breakthrough attacks even at 28 days after the last dose.

Although we observed improved efficacy and safety of garadacimab compared with placebo, some questions remain. Patients in the 600 mg garadacimab group had numerically lower reduction in the number of monthly attacks during the 12-week subcutaneous treatment period than did those in the both the 75 mg and 200 mg garadacimab groups. A post-hoc predicted response curve based on these data suggested a treatment effect in the 75 mg and 200 mg garadacimab groups compared with placebo, but that there was no additional efficacy benefit with 600 mg of garadacimab compared with 75 mg or 200 mg. Therefore, in our study, maximal

	Placebo group (n=8)	75 mg garadacimab group (n=9)	200 mg garadacimab group (n=8)	600 mg garadacimab group (n=7)
Number of treatment-emergent adverse events	12	11	18	24
Had at least one treatment-emergent adverse event	6 (75%)	6 (67%)	7 (88%)	7 (100%)
Any serious treatment-emergent adverse event	0	0	0	0
Severity of treatment-emergent adverse event				
Mild	5 (63%)	4 (44%)	5 (63%)	6 (86%)
Moderate	2 (25%)	3 (33%)	5 (63%)	3 (43%)
Severe	0	0	0	0
Treatment-emergent adverse event leading to study discontinuation	0	0	0	0
Treatment-emergent adverse event determined to be treatment related	2 (25%)	2 (22%)	1 (13%)	5 (71%)
Infection and infestations	3 (38%)	3 (33%)	5 (63%)	1 (14%)
General disorders and administration site conditions	2 (25%)	1 (11%)	1 (13%)	5 (71%)
Injection site reactions*	2 (25%)	1 (11%)	1 (13%)	4 (57%)
Skin and subcutaneous tissue disorders	1 (13%)	2 (22%)	2 (25%)	2 (29%)
Nervous system disorders	1 (13%)	0	1 (13%)	2 (29%)
Gastrointestinal disorders	1 (13%)	1 (11%)	2 (25%)	1 (14%)
Musculoskeletal and connective tissue disorders	1 (13%)	1 (11%)	0	0
Respiratory, thoracic, and mediastinal disorders	0	0	1 (13%)	2 (29%)
Injury, poisoning, and procedural complications	1 (13%)	1 (11%)	0	1 (14%)
Psychiatric disorders	0	0	1 (13%)	0
Immune system disorders	0	0	0	1 (14%)
Renal and urinary disorders	0	0	0	1 (14%)

Data are number of events or number of patients who experienced events presented as n (%). Adverse events are listed by MedDRA System Organ Class, except injection site reactions. A table of all adverse events, including MedDRA system organ class and preferred terms, occurring during the 12-week subcutaneous treatment period is in the appendix (p 6). MedDRA=Medical Dictionary for Regulatory Activities. *Preferred terms that are considered injection site reactions were selected on the basis of clinical judgement and are also reported in their original MedDRA System Organ Class as general disorders and administration site conditions.

Table 2: **Summary of adverse events occurring during the 12-week subcutaneous treatment period**

efficacy was at 200 mg every 4 weeks, and an increase to 600 mg did not appear to result in an increase in efficacy.

Although similar safety and efficacy with regards to the primary endpoint were seen with 75 mg and 200 mg garadacimab, better responses in the 200 mg garadacimab group to secondary endpoints (use of rescue medication, proportion of patients who were attack-free) suggest that the 200 mg dose might offer patients the optimal benefit–risk profile compared with 75 mg and 600 mg doses. A study in a larger patient population is needed to further assess the efficacy and safety of 200 mg garadacimab.

Several therapies, including other monoclonal antibodies, are available as prophylactic treatments for patients with hereditary angioedema.[23,24] However, garadacimab offers patients a valuable alternative because of two key features. First, garadacimab has a unique mechanism of action whereby, unlike other therapies for hereditary angioedema,[23,24] it inhibits FXII at the beginning of the kallikrein–kinin system, counteracting the dysregulation that occurs as a result of deficient C1-INH.[4,5,9] Second, garadacimab has a longer dosing interval than other prophylactic therapies,[23,24] reducing the burden of frequent injections for patients. Together, the unique mechanism of action of garadacimab and its monthly dosing regimen could offer an innovative alternative option for the prophylactic treatment and management of hereditary angioedema.

Our study also has several limitations. First, the study included only a small patient population because hereditary angioedema is a rare disease. Second, the patient population was mostly White and so, although data from previous hereditary angioedema studies do not suggest that race has an effect on treatment,[25] further data are required to ensure these results can be generalised across patient groups. Finally, the study results were only derived from a 12-week observation period, preventing any assessment of the long-term safety and efficacy of garadacimab.

Long-term prophylactic treatment of hereditary angioedema—namely, reducing attack frequency and improving quality of life—is becoming a reachable goal thanks to pharmacological therapies that target the bradykinin-producing cascade.[17,23] This study provides the first clinical evidence and a proof of concept for FXIIa inhibition as a novel strategy for hereditary angioedema prophylaxis. Garadacimab, a first-in-class recombinant monoclonal antibody targeting FXIIa, was efficacious and well tolerated when subcutaneously administered every 4 weeks over a period of 12 weeks. Further confirmation of the efficacy and safety of garadacimab in a phase 3 study is warranted.

Contributors

TC, MM, DSL, AR, WRL, IM-S, JSJ, WHY, BR, EA-P, PKK, and PB contributed to data validation and reviewed and provided input on the manuscript. HF, IJ, IP, MKD, and DP contributed to study conceptualisation, formal analysis, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, data validation, visualisation, and reviewed and provided input on the manuscript. TC, MM, DSL, AR, WRL, IM-S, JSJ, WHY, BR, EA-P, PKK, and PB were investigators in the clinical trial. All authors reviewed and edited the manuscript and participated in the decision to submit it for publication. HF and IP accessed and verified the underlying study data.

Declaration of interests

TC 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, the Board of Directors for the Mid-Atlantic American Lung Association, and the Board of Directors for the American Academy of Allergy, Asthma and Immunology. EA-P has received honoraria as a speaker or advisor from Adverum Biotechnologies, BioCryst, BioMarin, Centogene, CSL Behring, KalVista, Pharming, Pharvaris, and Shire/Takeda; and has received grants or clinical trial investigator support from BioCryst, CSL Behring, KalVista, Pharvaris, and Shire/Takeda. PB has consulted for CSL Behring, Takeda, Pharming, Pearl Therapeutics, BioCryst, CVS Health, Novartis, AstraZeneca and GlaxoSmithKline; and has received clinical trial support from CSL Behring, Takeda, BioCryst, and Novartis. MKD and DP are former full-time employees of CSL Behring and own stocks in CSL Behring. HF, IJ, and IP are full-time employees of CSL Behring and own stocks in CSL Behring. JSJ is a speaker for Takeda/Shire, CSL Behring, Teva, AstraZeneca, GlaxoSmithKline, Sanofi Genzyme, and Regeneron; and has received research funding or consultancy fees from CSL Behring, Takeda/Shire, BioCryst, Novartis, Genentech, AstraZeneca, Allakos, Fresenius Kabi, GlaxoSmithKline, and Regeneron. PKK is or recently was a speaker or an advisor for ALK Pharma, AstraZeneca, CSL Behring, GlaxoSmithKline, Kaleo, Merck, Mylan, Novartis, Pediapharm/Medexus, Sanofi and Takeda/Shire; and has received research funding from CSL Behring, Green Cross, and Takeda/Shire. DSL is a speaker, researcher, and consultant for CSL Behring, Takeda, Pharming, BioCryst, and Grifols. WRL is a speaker for CSL Behring, Pharming, AstraZeneca, Sanofi/Regeneron, GlaxoSmithKline, and Shire/Takeda; has served as a consultant for BioCryst, BioMarin, CSL Behring, Fresenius Kabi, Intellia, KalVista, Pharming, Pharvarius, and Shire/Takeda; is a board member of the US Hereditary Angioedema Association Medical Advisory Board; and has received grants or research support from ALK, BioCryst, CSL Behring, Ionis, Gossamer, KalVista, Kedrion, Therapure, and Takeda/Shire. 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, Shire/Takeda, Pharming, BioCryst, Novartis, Octapharma, and KalVista. IM-S has received honoraria, research funding, and travel grants from BioCryst, CSL Behring, Pharming, Octapharma, KalVista, and Takeda/Shire. IM-S served as a consultant for BioCryst, CSL Behring, Pharming, Octapharma, KalVista, and Takeda/Shire; and participated in advisory boards for BioCryst, CSL Behring, Pharming, Octapharma, KalVista, and Takeda/Shire. AR is a speaker, researcher, and advisor for CSL Behring, Takeda/Shire, BioCryst, Pharming, and Shulov Innovative Science. BR has been a speaker and advisory board member for CSL Behring and Takeda and has not received personal reimbursement for these activities; has participated in multiple clinical trials involving investigational drugs for CSL Behring, Takeda, BioCryst, Dyax, and Pharming and he does not hold patents or investments with these companies or involving this product; and he serves as a volunteer medical scientific advisor to the patient organisation Hereditary Angioedema Canada. WHY has received fees for consulting services from CSL Behring, Takeda/Shire, Novartis, Sanofi Genzyme, and Merck, and research grants from CSL Behring, Takeda/Shire, BioCryst, Pharming, AstraZeneca, Novartis, Sanofi Genzyme, Regeneron, Galderma, AnaptysBio, Glenmark, ALK Pharma, and Dermira.

Data sharing

CSL will only consider requests to share individual patient data that are received from systematic review groups or bona-fide researchers. CSL will not process or act on requests until 12 months after Article publication on a public website. A request will not be considered by CSL unless the proposed research question seeks to answer a significant

and unknown medical science or patient care question. Applicable country-specific privacy and other laws and regulations will be considered and might prevent sharing of individual patient data. Requests for use of individual patient data will be reviewed by an internal CSL review committee. If the request is approved, and the researcher agrees to the applicable terms and conditions in a data-sharing agreement, individual patient data that have been appropriately anonymised will be made available. Supporting documents, including the study protocol and statistical analysis plan, will also be provided. For information on the process and requirements for submitting a voluntary data sharing request for individual patient data, please contact CSL at clinicaltrials@cslbehring.com.

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