Original Article

Fixed-Dose Subcutaneous C1-Inhibitor Liquid for Prophylactic Treatment of C1-INH-HAE: SAHARA Randomized Study

William R. Lumry, MD[a], Inmaculada Martinez-Saguer, MD[b], William H. Yang, MD[c], Jonathan A. Bernstein, MD[d], Joshua Jacobs, MD[e], Dumitru Moldovan, MD[f], Marc A. Riedl, MD, MS[g], Douglas T. Johnston, DO[h], H. Henry Li, MD[i], Yongqiang Tang, PhD[j,*], Jennifer Schranz, MD[j,*,†], Peng Lu, MD[j], Moshe Vardi, MD[j], and Henriette Farkas, MD[k]; for the SAHARA study group *Dallas, Tex; Mörfelden-Walldorf, Germany; Ottawa, Ontario, Canada; Cincinnati, Ohio; Walnut Creek, San Diego, Calif; Târgu Mureş, Romania; Charlotte, NC; Chevy Chase, Md; Lexington, Mass; Budapest, Hungary*

What is already known about this topic? C1 inhibitor (C1-INH) is a first-line treatment for long-term hereditary angioedema (HAE) attack prevention.

What does this article add to our knowledge? Subcutaneous fixed-dose plasma-derived C1-INH liquid is safe and effective in HAE prophylaxis.

How does this study impact current management guidelines? A fixed-dose, subcutaneously administered, safe, and effective prophylactic treatment may improve patients' experience.

[a]AARA Research Center, Dallas, Texas
[b]Hämophilie-Zentrum Rhein Main (HZRM), Mörfelden-Walldorf, Germany
[c]Ottawa Allergy Research Corporation, University of Ottawa Medical School, Ottawa, Ontario, Canada
[d]Bernstein Clinical Research Center, Cincinnati, Ohio
[e]Allergy and Asthma Clinical Research, Walnut Creek, Calif
[f]MediQuest Medical Center, Sangeorgiu de Mures, Târgu Mureş, Romania
[g]University of California, San Diego, Calif
[h]Asthma & Allergy Specialists, PA, Charlotte, NC
[i]Institute for Asthma and Allergy, Chevy Chase, Md
[j]Shire, now part of Takeda, Lexington, Mass
[k]Hungarian Angioedema Reference Center, Semmelweis University, Budapest, Hungary
* These authors were employees of Shire (now part of Takeda) at the time of this analysis.
† Current affiliation: Nabriva Therapeutics, King of Prussia, Pa.

The SAHARA study was sponsored by Shire Human Genetic Therapies, Inc., a Takeda company. Under the direction of the authors, Sophia Shumyatsky, PharmD, employee of Excel Medical Affairs, provided writing assistance for this manuscript. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by Excel Medical Affairs. Shire Human Genetic Therapies, Inc., a Takeda company, provided funding to Excel Medical Affairs for support in writing and editing this manuscript. The interpretation of the data was made by the authors independently.

Conflicts of interest: W. R. Lumry has received consultant fees from Adverum, BioCryst, CSL Behring, Pharming, and Shire (a Takeda company); research grants from BioCryst, CSL Behring, Pharming, and Shire (a Takeda company); payments for lectures from CSL Behring, Pharming, and Shire (a Takeda company); and is a member of the Medical Advisory Board of the US Hereditary Angioedema Association. I. Martinez-Saguer has received honoraria, research funding, and travel grants from BioCryst, CSL Behring, Pharming, and Shire (a Takeda company) and/or served as a consultant and/or participated in advisory boards for these companies. W. H. Yang is a consultant and member of the advisory board for CSL Behring and Shire (a Takeda company); has received unrestricted educational grants from AnaptysBio, BioCryst, CSL Behring, Novartis, and Shire (a Takeda company); and research grants from Aimmune, AstraZeneca, BioCryst, CSL Behring, DBV Technologies, Galderma, Genentech/Roche, GlaxoSmithKline, Merck, Pfizer, Pharming, Regeneron, Sanofi-Genzyme, and Shire (a Takeda company). J. A. Bernstein has been a clinical investigator for BioCryst, CSL Behring, Pharming, and Shire (a Takeda company); a speaker for CSL Behring, Pharming, and Shire (a Takeda company); and a consultant for BioCryst, CSL Behring, Pharming, and Shire (a Takeda company). J. Jacobs has received research grants from 3M, Aimmune, AstraZeneca, CSL Behring, Genentech, Novartis, Sanofi, Shire (a Takeda company), and Teva; consulting fees from AstraZeneca, CSL Behring, Pharming, Regeneron, Shire (a Takeda company), and Teva; and speaker honoraria from Shire and Teva. D. Moldovan has served as clinical investigator for BioCryst, CSL Behring, Pharming, and Shire (a Takeda company); a consultant for CSL Behring, Octapharma, Pharming, and Shire (a Takeda company); and has received travel grants from CSL Behring, Pharming, Shire (a Takeda company), and Swedish Orphan Biovitrum. M. A. Riedl has received research grants from BioCryst, CSL Behring, Pharming, and Shire (a Takeda company); consulting fees from Adverum, Alnylam, BioCryst, CSL Behring, Ionis, Pharming, and Shire (a Takeda company); payments for lectures from CSL Behring, Pharming, and Shire (a Takeda company); and is a medical advisory board member of the US HAE Association. D. T. Johnston has served on advisory boards for CSL Behring, Pharming/Valeant, and Shire (a Takeda company); received speaker fees from Shire (a Takeda company); and has served as an investigator for BioCryst and Shire (a Takeda company). H. H. Li has been a clinical investigator and received grants and/or honoraria from BioCryst, CSL Behring, Pharming, and Shire (a Takeda company). Y. Tang and J. Schranz were full-time employees of Shire (a Takeda company) at the time of this analysis. P. Lu and M. Vardi are full-time employees of Shire (a Takeda company). H. Farkas has received honoraria and travel grants from BioCryst, CSL Behring, Pharming, Shire (a Takeda company), and Swedish Orphan Biovitrum and/or served as a consultant for these companies.

Received for publication August 31, 2018; revised December 12, 2018; accepted for publication January 6, 2019.
Available online January 23, 2019.
Corresponding author: William R. Lumry, MD, AARA Research Center, 10100 N. Central Expressway, Suite 100, Dallas, TX 75231. E-mail: LumryMD@AllergySpecialists.us.
2213-2198
© 2019 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
https://doi.org/10.1016/j.jaip.2019.01.021

Abbreviations used

AE- Adverse event
AUC- Area under the plasma concentration-time curve
AUC_{0-96}- Area under the plasma concentration-time curve from time zero to last measurable concentration
AUC_{0-t}- Area under the plasma concentration-time curve from time zero extrapolated to the end of the dosing interval tau
C1-INH- C1 esterase inhibitor
C1-INH-HAE- Hereditary angioedema with C1 inhibitor deficiency
CI- Confidence interval
C_{max}- Maximum observed plasma concentration
C_{min}- Minimum observed plasma concentration
eCRF- Electronic case report form
HAE- Hereditary angioedema
ICH- International Council for Harmonisation
IRT- Interactive response technology
ISR- Injection site reaction
IV- Intravenous
LS- Least squares
NNA- Normalized number of attacks
PD- Pharmacodynamics
pdC1-INH- Plasma-derived C1 esterase inhibitor
PK- Pharmacokinetics
SAE- Serious adverse event
SC- Subcutaneous
SD- Standard deviation
TEAE- Treatment-emergent adverse event
T_{max}- Time of maximum observed plasma concentration

BACKGROUND: Hereditary angioedema (HAE) with C1 inhibitor deficiency (C1-INH) is characterized by swelling of subcutaneous and/or submucosal tissues.

OBJECTIVE: To evaluate efficacy/safety of fixed-dose subcutaneous plasma-derived C1-INH (pdC1-INH) liquid for HAE attack prevention (NCT02584959).

METHODS: Eligible patients were ≥12 years with ≥2 monthly attacks prescreening or pre—long-term prophylaxis. In a partial crossover design, 80% of patients were randomized to placebo or pdC1-INH liquid for 14 weeks and crossed over from active to placebo or vice versa for another 14 weeks. The remainder were randomized to pdC1-INH liquid for 28 weeks. The primary efficacy endpoint was normalized number of attacks (NNA) versus placebo. Key additional endpoints were the proportion of patients achieving NNA reduction ≥50%, attack severity, number of attack-free days, and safety.

RESULTS: Seventy-five patients were randomized and 58 (77%) completed the study. Mean age 41 years; 88% HAE type I. Least-squares means of NNA were reduced from 3.9 with placebo to 1.6 with pdC1-INH (from day 1; $P < .0001$). Most patients had ≥50% NNA reduction with pdC1-INH (from day 1, 78%). A total of 8.8% of placebo-treated patients were attack-free and 5.3%, 22.8%, and 63.2% had mild, moderate, and severe attacks, respectively; 37.5% of pdC1-INH—treated patients were attack-free and 8.9%, 26.8%, and 26.8% had mild, moderate, and severe attacks, respectively. Treatment-emergent adverse event rates were similar between groups (52% vs 56% for pdC1-INH crossover vs placebo, respectively).

CONCLUSIONS: Fixed-dose subcutaneous pdC1-INH liquid was superior to placebo in preventing HAE attacks and demonstrated a favorable safety profile. **© 2019 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).** **(J Allergy Clin Immunol Pract 2019;7:1610-8)**

Key words: *Hereditary angioedema; Subcutaneous; Fixed-dose; Liquid; SAHARA study; Long-term prophylactic treatment*

Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare genetic disease caused by *SERPING-1* gene mutations, resulting in a deficiency (type I) or dysfunction (type II) in the C1 esterase inhibitor (C1-INH) protein.[1] Worldwide the prevalence of diagnosed cases is approximately 1.5 per 100,000 (equivalent to approximately 1 in 67,000).[2] C1-INH regulates the key components of the kallikrein-kinin cascade; C1-INH deficiency is thus an important underlying factor in HAE pathogenesis.[3] Dysregulated activation of the contact system leads to uninhibited production of the vasodilator bradykinin, which promotes vascular permeability and subsequently causes local tissue swelling and pain.[1,3]

C1-INH-HAE manifests as swelling of subcutaneous or submucosal tissues,[4] including the gastrointestinal tract, extremities, and upper airways.[4,5] Attacks occluding the upper airway can cause death by asphyxiation.[6] Symptoms recur with unpredictable frequency and intensity throughout patients' lives, often in the absence of triggers or prodromes.[6,7] C1-INH-HAE negatively impacts patients' physical health and emotional well-being (both during and in between attacks), limits education and work opportunities, and hinders participation in social activities.[6,8-11]

For many patients, long-term prophylaxis of HAE attacks is a lifelong requirement.[12] The treatment approach should be individualized based on disease frequency, severity, impact on daily life, and patient preference.[13] The need to begin or continue long-term prophylaxis should be re-evaluated at each patient visit.[13] C1-INH is recommended as a first-line therapy for the prevention of HAE attacks.[13] The intravenous (IV) plasma-derived nanofiltered C1-INH concentrate Cinryze (C1 Esterase Inhibitor [Human], Shire Services BVBA, Brussels, Belgium [EU]; Shire ViroPharma Inc., Lexington, Mass) has an established long-term safety and efficacy profile for the prophylactic treatment against HAE attacks in patients with C1-INH-HAE.[14-17]

Pharmacodynamic (PD) findings from a double-blind, randomized study evaluating the treatment of acute HAE attacks with IV-administered, plasma-derived nanofiltered C1-INH demonstrated significant increases ($P < .0001$) versus placebo in antigenic C1-INH levels (between-treatment difference 9.2 [95% confidence interval (CI), 5.3-13.2]) and functional C1-INH levels (between-treatment difference 37.2 [95% CI, 29.2-45.3]) during the first 4-hour postadministration observation period. However, significant differences between groups were not noted in C4 values (−0.2 [95% CI, −2.4 to 2.0; $P = .86$]).[16] Pharmacokinetic (PK) findings from a randomized, open-label PK study demonstrated a non—dose-proportional increase with a single dose (1000 U) versus double dose (1000 U, followed by a second 1000 U dose 1 hour later) of IV-administered, plasma-derived nanofiltered C1-INH in maximum plasma concentration (mean maximum observed plasma concentration [C_{max}]; from 0.31 ± 0.20 U/mL at baseline to 0.68 ± 0.08 U/mL with the single dose, and from 0.33 ± 0.20 U/mL at baseline to 0.85 ± 0.12 with the double dose).[18]

On a long-term basis, IV administration poses various challenges, particularly for patients in whom peripheral vein access is difficult.[19] The subcutaneous (SC) administration route is a more convenient and feasible alternative for long-term prophylaxis.[13]

Findings from the phase 3 COMPACT study demonstrated significantly favorable efficacy versus placebo with weight-based, SC-administered, human plasma–derived C1-INH (Haegarda; CSL Behring GmbH, Marburg, Germany) in patients with C1-INH-HAE.[20] This agent was recently approved for routine prophylaxis against HAE attacks in adolescent and adult patients.[21] The phase 3 SAHARA study (SubcutAneous proPHylactic C1-INH for hereditARy Angioedema) evaluated a fixed-dose, ready-to-use, SC-administered plasma-derived C1-INH liquid (pdC1-INH liquid [SHP616]) for the prophylactic treatment of patients with C1-INH-HAE.

METHODS

Study overview

Patients were enrolled from 33 sites in North America and Europe. Screening began December 17, 2015, and the last patient completed treatment on July 24, 2017.

Study design

The SAHARA study was a randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT02584959). Patients were randomized in a 2:2:1 ratio to receive pdC1-INH liquid or placebo in partial crossover sequences over two 14-week treatment periods as follows: pdC1-INH liquid in period 1, crossover to placebo in period 2; placebo in period 1, crossover to pdC1-INH liquid in period 2; or continuous pdC1-INH liquid for 28 weeks (to evaluate long-term safety). The actual treatment sequence for each patient was determined by a randomization schedule automatically assigned using interactive response technology (IRT). Patients were stratified by whether they received versus did not receive long-term prophylaxis with C1-INH at the time of enrollment.

This study followed the International Council for Harmonisation (ICH) of Good Clinical Practice and the Declaration of Helsinki. All applicable local ethical and legal requirements were met and patients provided informed consent and assent. Procedures were compliant with ICH guidelines, requirements of the local institutional review board (IRB) or independent ethics committee (IEC), and state and local law. The IRB or IEC approved all protocols and protocol amendments, informed consent and assent forms, patient recruitment, and relevant supporting information.

Patients

Patients were screened within 21 days before randomization. Eligible patients were ≥12 years of age (or ≥18 years in Germany and Israel); had a diagnosis of HAE type I or II and functional C1-INH level <50% of normal; experienced an average of ≥2.0 HAE attacks per month during the 3 consecutive months before use of long-term prophylactic treatment or before screening (no time limit provided); and were willing to receive treatment with icatibant for acute attacks (for patients ≥18 years old).

Adults receiving prophylactic IV C1-INH at doses >1000 IU every 3 or 4 days (or weekly dose >2000 IU) or adolescents currently receiving C1-INH for prophylaxis were excluded. However, no restrictions were imposed regarding the lack of response to prior C1-INH therapy. Additional exclusions were the presence of an HAE attack within 2 days before the first dose of study drug in treatment period 1; receipt of any C1-INH therapy or blood product for HAE treatment or prevention within 3 days before the first dose of study drug in treatment period 1; history of hypercoagulability or other predisposition for thromboembolism; or diagnosis of the acquired angioedema or known presence of anti–C1-INH antibodies.

Treatments and visits

For each of the two 14-week treatment periods, patients received fixed-dose (2000 IU) pdC1-INH liquid or placebo in a double-blind manner via SC injection in the abdomen twice weekly (every 3 or 4 days), with no washout between treatment periods. pdC1-INH liquid was supplied in clear glass vials containing 1000 IU C1-INH in 2 mL sterile liquid. Placebo was supplied in the identical 2-mL presentation (including excipients) without the C1-INH protein. Two vials of each agent (4 mL) were required per each respective dose. No reconstitution was needed.

During both treatment periods, pdC1-INH liquid or placebo was administered at the study site on dosing visits 1, 8, 16, 24, and 28. The remaining doses were administered at various locations by qualified personnel or home health professionals, or by the patient or their caregivers (after appropriate training). Compliance was captured either by the site personnel or patient or home health professional, depending on whether the injection was administered at the study site or at home. For self-administered doses, date and time of injection, and dose completion (complete vs partial administration quantity) were captured in a dedicated electronic case report form (eCRF) integrated in the electronic diary. In addition, the principal investigator, study site personnel, or qualified home health professional ensured that all documentation (including receipt, storage, dispensing, loss/damaged, and return of used/unused product) was complete. Post-treatment visits occurred 1 week (±1 day) and 1 month (±2 days) after the last dose of study drug in treatment period 2 for follow-up safety assessments. When possible, all patients who discontinued the study completed the follow-up safety visits. Each patient participated in the study for approximately 9 months.

Per protocol, for the treatment of acute attacks, patients ≥18 years old were to receive icatibant as first-line therapy. For patients ≥12 to <18 years old, or for those who continued to require the treatment of an acute attack after receiving icatibant, other standard-of-care therapy was to be provided per locally approved product information, including plasma-derived and recombinant C1-INH or ecallantide.

Blinding

All study site personnel, patients, home-care providers, and the sponsor were blinded to treatment sequence. To maintain blinding, PK and PD findings were kept in strict confidence by the independent external laboratory performing the analyses until study unblinding. A limited number of study sponsor representatives responsible for the IRT and product labeling were unblinded to treatment assignment to review drug accountability on an ongoing basis.

Study endpoints

The prespecified primary endpoint was monthly normalized number of HAE attacks (NNA) during a treatment period, starting from day 1. This was expressed as follows: NNA = 30.4 days × (number of attacks during treatment period/days of treatment period). NNA was analyzed using a linear mixed-effect model. The mean treatment difference for pdC1-INH liquid versus placebo was estimated with 95% CIs. The analysis of NNA in a treatment period included data from weeks 1 to 14. The null hypothesis to be tested was that NNA with pdC1-INH liquid was greater than or equal to

TABLE I. Patient demographics, baseline characteristics, and historical HAE attack characteristics*

Characteristic†	Crossover 2000 IU pdC1-INH/placebo‡ (n = 60)	Continuous 2000 IU pdC1-INH (n = 15)	Total (N = 75)
Mean (SD) age, y§	40.6 (14.1)	44.4 (16.4)	41.3 (14.6)
Female, n (%)	44 (73.3)	8 (53.3)	52 (69.3)
White, n (%)	57 (95.0)	15 (100.0)	72 (96.0)
Mean (SD) weight, kg	83.1 (26.7)	87.9 (26.5)	84.0 (26.5)
HAE type I, n (%)	52 (86.7)	14 (93.3)	66 (88.0)
Received HAE therapy during last 12 mo, n (%)	54 (90.0)	14 (93.3)	68 (90.7)
Received LTP with C1-INH or androgens any time before screening, n (%)	30 (50.0)	8 (53.3)	38 (50.7)
Received LTP until randomization, n (%)	15 (25.0)	6 (40.0)	21 (28.0)
C1-INH	9 (15)	4 (26.7)	13 (17.3)
Oral androgens	6 (10)	2 (13.3)	8 (10.7)
No treatment	45 (75.0)	9 (60.0)	54 (72.0)
Location of HAE attacks during 3 consecutive mo before screening, n (%)‖			
Gastrointestinal/abdominal	53 (88.3)	11 (73.3)	64 (85.3)
Extremity or peripheral	48 (80.0)	11 (73.3)	59 (78.7)
Genitourinary	20 (33.3)	4 (26.7)	24 (32.0)
Facial	18 (30.0)	6 (40.0)	24 (32.0)
Upper airway	15 (25.0)	2 (13.3)	17 (22.7)

C1-INH, C1 esterase inhibitor; *HAE*, hereditary angioedema; *LTP*, long-term prophylaxis; *pdC1-INH*, plasma-derived C1 esterase inhibitor; *SD*, standard deviation.
*Based on patients in the safety set (all patients who received ≥1 dose of study drug).
†The baseline value was the last observation before or on the first dose date of treatment period 1.
‡Total combined dosages of both 2000 IU pdC1-INH liquid/placebo and placebo/2000 IU pdC1-INH liquid sequences.
§Age was reported at the date of informed consent.
‖Each patient was counted only once per category in typical location of attacks. Patients could have been counted more than once if their typical attack involved multiple locations.

NNA with placebo. Patients in crossover sequences with ≥1 post-baseline observation were analyzed for efficacy.

Key prespecified secondary endpoints included (1) the proportion of patients achieving a ≥50% reduction in NNA during the pdC1-INH liquid treatment period relative to the placebo period (ie, clinical response) from day 1, (2) NNA excluding first 2 weeks of each treatment period, and (3) the proportion of patients achieving a ≥50% reduction in NNA with pdC1-INH liquid relative to placebo, excluding the first 2 weeks of each treatment period. Exclusion of the first 2 weeks of treatment reflects the effect of intervention versus placebo at a steady state. For the responder analyses, the null hypothesis was that the proportion of patients achieving a ≥50% reduction in NNA is ≤0.2 (using the lower limit of the 95% CI as the threshold).

Additional prespecified secondary endpoints included the proportion of patients achieving a ≥50%, ≥70%, ≥90%, and 100% reduction, as well as reduction to <1 NNA during a treatment period relative to pretreatment assessment. Severity of HAE attacks, monthly normalized attacks requiring acute treatment, and monthly number of attack-free days were also evaluated. Categories for maximum attack severity per treatment period included no, mild, moderate, and severe symptoms. *Cumulative attack severity* was defined as the sum of maximum symptom severities recorded for each HAE attack in a treatment period for each patient. *Cumulative daily severity* was defined as the sum of all daily severities in a treatment period for each patient, with *daily severity* defined as the maximum severity across all anatomic locations in a given day for the corresponding attack. Patient-reported outcomes were also assessed but are not reported here.

The safety/tolerability, immunogenicity, and occurrence of injection site reactions (ISRs) were also assessed. Injection sites were evaluated on predefined site visits by qualified site personnel for erythema and swelling and the presence of cutaneous pain, burning sensation, itching/pruritus, and warm sensation. The diameter of any erythema or swelling was measured to obtain severity grading. Patient experience with self-administration of pdC1-INH liquid was also evaluated. ISRs were not assessed during home administration. These cases were captured only if they met the threshold for a serious adverse event (SAE).

PK/PD of functional C1-INH binding activity, plasma C1-INH antigen levels, and complement C4 concentrations in study patients were exploratory endpoints, including area under the plasma concentration-time curve (AUC), C_{max}, time of maximum observed plasma concentration, and minimum observed plasma concentration (C_{min}).

Assessments

Patients recorded HAE symptoms and their experience with self-administration using electronic diaries. Investigators completed an eCRF for each attack, including date and time of onset and complete resolution of symptoms and characterization, location, and severity of swelling. Adverse events (AEs) were recorded from the screening phase through 7 days after the last dose of study drug. Also, all SAEs occurring through 30 days after the last dose of study drug were reported. Additional safety assessments included vital signs, clinical laboratory measurements (eg, biochemistry, complement testing), and electrocardiograms. Patients were monitored for the development of C1-INH antibodies and, if present, were further evaluated for neutralizing antibodies. ISRs were recorded in the eCRF for local tolerability after SC administration.

Serial predose blood samples were collected at baseline and during select treatment visits (specified in Table E1, available in this article's Online Repository at www.jaci-inpractice.org) to determine plasma concentrations of C1-INH antigen, functional C1-INH binding

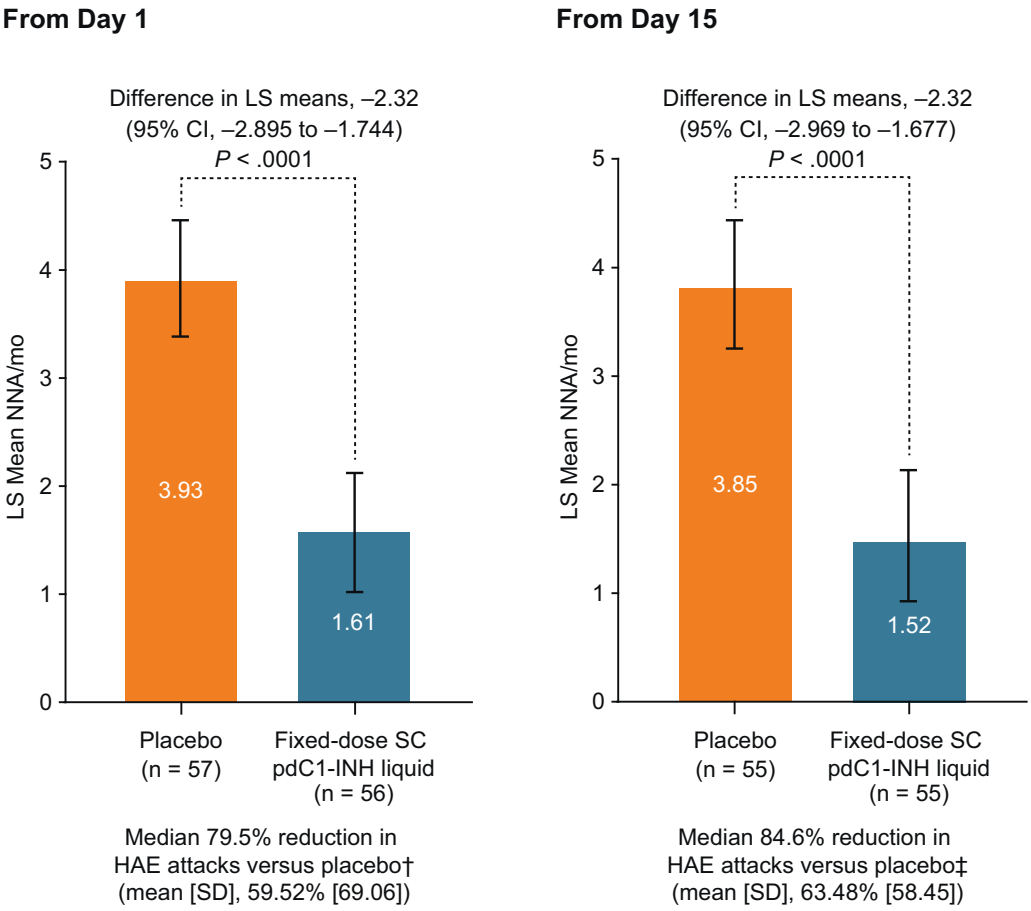

FIGURE 1. Normalized number of HAE attacks during treatment periods. Based on the full analysis set from the crossover sequences, consisting of all patients in the safety set who received ≥1 postbaseline (eg, randomization) primary efficacy assessment. *CI*, Confidence interval; *HAE*, hereditary angioedema; *LS*, least squares; *NNA*, normalized number of attacks; *pdC1-INH*, plasma-derived C1-INH; *SD*, standard deviation. †Reflects the entire study period. ‡Reflects the steady state period.

activity, and plasma complement C4 concentrations. Blood sample collection times for PK/PD assessments are shown in Table E1. Serum samples were collected before the first dose of study drug on visit 1a (dose 1 of treatment period 1), visit 1b (dose 1 of treatment period 2), and throughout both treatment periods for the analysis of anti−C1-INH antibodies.

At various times throughout the study, patients were asked to rate their overall experience with twice-weekly SC injections. Responses were entered into the electronic patient diary.

Determination of sample size

The enrollment goal was to randomize ≥66 patients to ensure that 54 patients completed both treatment periods (44 for crossover sequences, 10 for active/active sequence). For the primary efficacy endpoint (NNA), a sample of 44 patients would provide 90% power at an alpha level of 0.025 (1-sided) to detect a difference of 1.0 attack per month between active treatment and placebo, assuming a standard deviation (SD) of the difference of 2.0. For the key secondary endpoints, 44 patients would provide 90% power to test the null hypothesis that the proportion of patients achieving ≥50% reduction in NNA with pdC1-INH liquid versus placebo is ≤0.2, assuming that the true proportion is 0.44 by using a 1-group χ^2 test at an alpha level of 0.025 (1-sided).

A safety set of 60 patients ensured that if the true proportion of any patient with a particular event was ≥5%, then the probability of observing ≥1 event in the safety set was >95%.

Statistical analyses

Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC) Version 9.4. PK analysis was performed using Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ) Version 6.3. Continuous variables were summarized using descriptive statistics: n, mean, SD, median, minimum, and maximum. Categorical variables were summarized by number of patients (n) and percentage of patients per category.

To control for type 1 error, primary and key secondary endpoints were tested at the 0.05 significance level in the following prespecified order: primary endpoint, key secondary endpoint 1, key secondary endpoint 2, and key secondary endpoint 3. If 1 hypothesis test was not significant, the significance of all subsequent tests was not to be assessed. Determination of study success was based solely on results of the primary endpoint analysis regardless of results for key secondary endpoints.

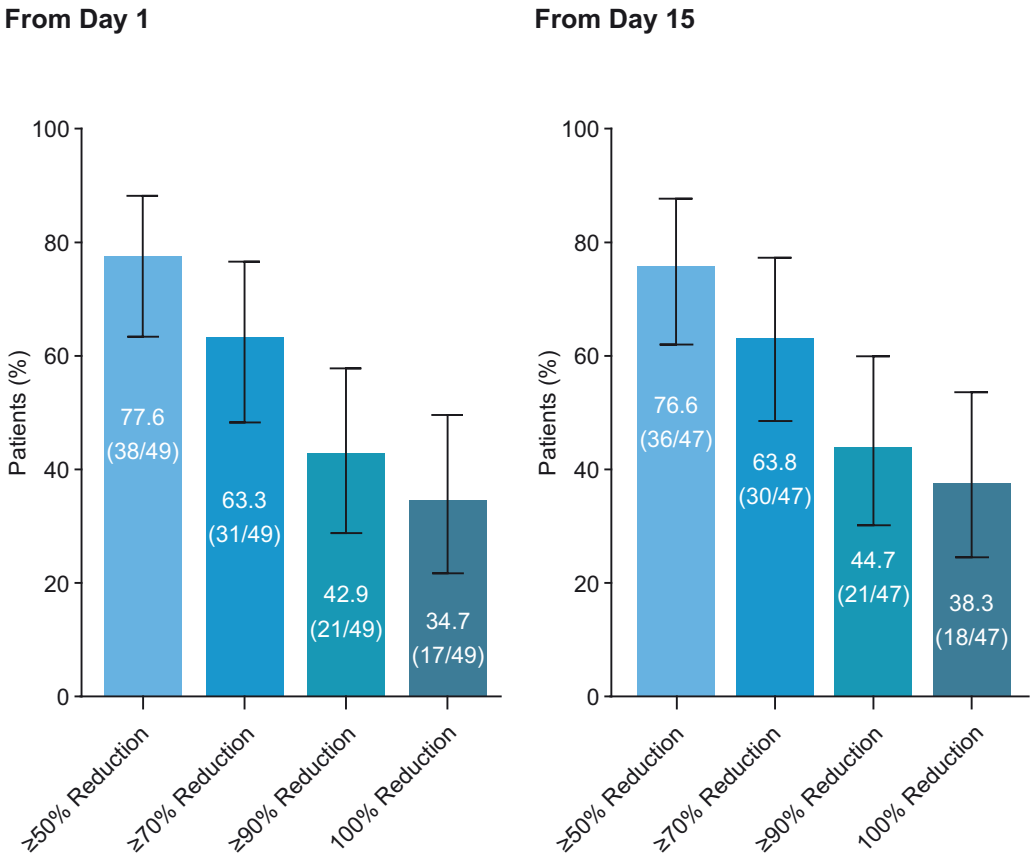

FIGURE 2. Proportion of patients achieving ≥50%, ≥70%, ≥90, and 100% reduction in NNA during treatment periods relative to placebo periods, from day 1 and from day 15. Clinical response (≥50% reduction in NNA vs placebo) was achieved by 77.6% and 76.6% of patients from days 1 and 15, respectively. Based on the full analysis set from the crossover sequences with patients who had data in both treatment periods. The proportion of patients achieving a reduction in normalized number of attacks with C1-INH liquid versus placebo was statistically significant for each category of response (from day 1: ≥50%, $P < .0001$; ≥70%, $P < .0001$; ≥90%, $P = .0005$; 100%, $P = .0233$; from day 15: ≥50%, $P < .0001$; ≥70%, $P < .0001$; ≥90%, $P = .0002$; 100%, $P = .0058$) relative to a predetermined efficacy threshold of 20%. Error bars represent 95% CI values. *CI*, Confidence interval; *NNA*, normalized number of attacks; *pdC1-INH*, plasma-derived C1-INH.

RESULTS

Eighty-one patients were screened, and 75 patients were randomized (60 for crossover sequence [n = 31 receiving pdC1-INH liquid in period 1; n = 29 receiving placebo in period 1], and 15 for continuous pdC1-INH liquid). Fifty-eight patients (77%) completed the study. The reasons for study discontinuation included patient withdrawal (n = 9), AEs (n = 4), physician decision (n = 1), lost to follow-up (in a patient who completed treatment; n = 1), and other (n = 2). One patient receiving pdC1-INH liquid experienced 2 treatment-emergent AEs (TEAEs) that led to treatment withdrawal (nausea and headache). Both events were considered treatment related and occurred within 24 hours of administration. Two patients receiving placebo experienced 2 TEAEs leading to withdrawal (one had cardiac arrest and the other had an HAE attack). Neither event was considered treatment related. Patient disposition is shown in Figure E1 (available in this article's Online Repository at www.jaci-inpractice.org).

Patients were generally representative of the overall HAE study population; baseline demographics and clinical characteristics were well balanced across treatment sequences (Table I). Mean age was 41.3 years. Most patients were white (96.0%), female (69.3%), and had HAE type I (88.0%). Most (90.7%) had received HAE therapy (for acute treatment or prophylaxis) within the last 12 months. Prophylactic treatment with C1-INH or androgens was used by 50.7% of patients at any time before screening, and by 28.0% of patients up until randomization. A mean of 11.9 attacks occurred within 3 consecutive months before screening.

Efficacy

Fifty-six and 57 of 60 patients from the crossover sequences received pdC1-INH and placebo, respectively, and were assessed for efficacy.

Normalized number of HAE attacks. Regardless of treatment sequence, least-squares (LS) means of the NNA were significantly lower for pdC1-INH liquid versus placebo (difference in LS means, −2.32, both from day 1 and day 15, $P < .0001$; Figure 1). There was a median 79.5% reduction in HAE attacks versus placebo from day 1 (mean [SD] 59.52% [69.06]) and 84.6% from day 15 (mean [SD] 63.48% [58.45]).

TABLE II. Clinical response, cumulative attack severity, and cumulative daily severity* compared with pretreatment

Endpoint	PdC1-INH liquid	Placebo	*P* value
Clinical response compared with pretreatment			
n†	53	55	
Achieving ≥50% reduction, n (%)	41 (77.4)	13 (23.6)	< .0001
Achieving ≥70% reduction, n (%)	35 (66.0)	9 (16.4)	< .0001
Achieving ≥90% reduction, n (%)	22 (41.5)	5 (9.1)	< .0001
Achieving 100% reduction, n (%)	18 (34.0)	5 (9.1)	.0005
Achieving reduction to <1 NNA, n (%)	33 (62.3)	6 (10.9)	< .0001
Cumulative HAE attack severity			
n	56	57	
Overall LS mean (95% CI)	3.159 (1.856-4.463)	8.041 (6.746-9.336)	
Difference in overall LS mean (95% CI)	−4.881 (95% CI: −6.113 to −3.649)		< .0001
Cumulative daily severity			
n	56	57	
Overall LS mean for cumulative daily severity	7.492 (2.928-12.056)	19.609 (15.067-24.151)	
Difference in overall LS mean (95% CI)	−12.117 (95% CI: −15.529 to −8.705)		< .0001

CI, Confidence interval; *HAE*, hereditary angioedema; *LS*, least squares; *NNA*, normalized number of attacks; *pdC1-INH*, plasma-derived C1 esterase inhibitor.
*Based on the full analysis set from the crossover sequences. The full analysis set consists of all patients in the safety set who received ≥1 postbaseline (eg, randomization) primary efficacy assessment.
†Patients with pretreatment and post-treatment NNA values.

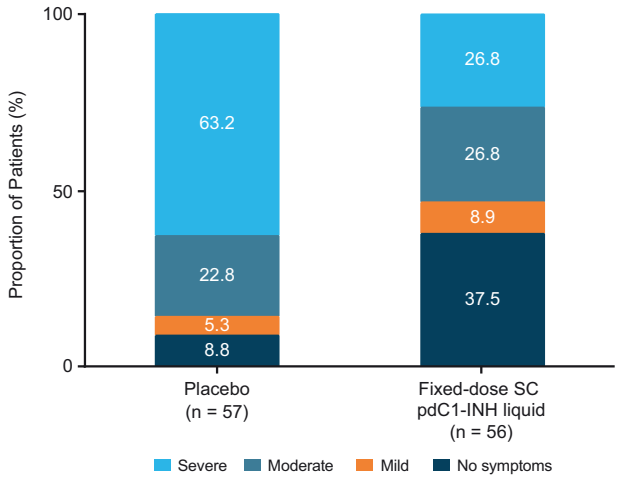

FIGURE 3. Maximum attack severity. Based on the full analysis set from the crossover sequences; not restricted to patients who improved or who had data from both treatment periods. Percentages may not total 100 because of rounding. *pdC1-INH*, Plasma-derived C1-INH; *SC,* subcutaneous.

Clinical response. The proportion of patients achieving clinical response with pdC1-INH liquid (≥50% reduction in NNA vs placebo) is shown in Figure 2. Of patients with data in both treatment periods, 77.6% and 76.6% receiving pdC1-INH liquid from days 1 and 15, respectively, were clinical responders ($P < .0001$).

Clinical response compared with pretreatment. The proportion of patients who achieved a clinical response relative to pretreatment assessment was significantly higher with pdC1-INH liquid versus placebo (Table II). Of 53 patients receiving pdC1-INH liquid and 55 patients receiving placebo with available pretreatment and post-treatment NNA values, 77.4% versus 23.6% achieved clinical response, respectively ($P < .0001$).

Attack severity. Maximum symptom severity for HAE attacks was generally lower for patients receiving pdC1-INH. Severe symptoms were experienced by 26.8% and 63.2% of patients receiving pdC1-INH liquid versus placebo, whereas 37.5% and 8.8%, respectively, had a maximum attack severity of 0 (ie, no symptoms; Figure 3). The median overall percentage reduction in normalized cumulative severity for pdC1-INH liquid versus placebo was 83.3% (95% CI, −97.67 to −74.47; $P < .0001$); the median overall percentage reduction in normalized cumulative daily severity was 83.7% (−99.09 to −73.33, $P < .0001$). Overall LS means are shown in Table II.

On average, patients receiving pdC1-INH liquid had a significantly greater number of attack-free days versus placebo (mean [95% CI] 26.788 [25.106-28.470] vs 21.353 [19.681-23.025]). The difference in overall LS means was 5.435 (95% CI, 3.981-6.889; $P < .0001$).

Number of angioedema attacks requiring acute treatment. Significantly fewer patients receiving pdC1-INH liquid versus placebo required acute treatment for HAE attacks (difference in overall LS means, −2.175, 95% CI, −2.750 to −1.599; $P < .0001$).

The occurrence of HAE attacks, attack severity, and use of on-demand medications for each patient are depicted in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org).

Safety and tolerability

Seventy-one patients received pdC1-INH liquid and were assessed for safety. For comparison with placebo, 56 and 57

TABLE III. TEAEs by system organ class and preferred term occurring in ≥5% of patients, n (%)*

TEAE, n (%)	Crossover arms (n = 56)	Placebo (n = 57)	pdC1-INH liquid overall (n = 71)†
Gastrointestinal disorders	7 (12.5)	4 (7.0)	9 (12.7)
Diarrhea	3 (5.4)	0 (0.0)	3 (4.2)
General disorders and administration site conditions	4 (7.1)	4 (7.0)	5 (7.0)
Infections and infestations	20 (35.7)	13 (22.8)	28 (39.4)
Viral upper respiratory tract infection	7 (12.5)	3 (5.3)	11 (15.5)
Upper respiratory tract infection	7 (12.5)	4 (7.0)	7 (9.9)
Injury, poisoning, and procedural complications	1 (1.8)	4 (7.0)	1 (1.4)
Contusion	0 (0.0)	3 (5.3)	0 (0.0)
Investigations	3 (5.4)	3 (5.3)	4 (5.6)
Fibrin D dimer increased	0 (0.0)	2 (3.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (3.6)	3 (5.3)	4 (5.6)
Nervous system disorders	8 (14.3)	7 (12.3)	10 (14.1)
Headache	6 (10.7)	6 (10.5)	6 (8.5)
Respiratory, thoracic, and mediastinal disorders	5 (8.9)	5 (8.8)	5 (7.0)
Epistaxis	3 (5.4)	0 (0.0)	3 (4.2)
Skin and subcutaneous tissue disorders	4 (7.1)	3 (5.3)	4 (5.6)

pdC1-INH, Plasma-derived C1 esterase inhibitor; *TEAE*, treatment-emergent adverse event.
*Percentages are based on the number of patients in the safety set for each treatment (all patients who received ≥1 dose of study drug).
†Patients in the active-active sequence (n = 15) received pdC1-INH liquid for 28 weeks.

patients from the crossover sequences who received pdC1-INH liquid and placebo, respectively, were evaluated.

TEAEs. A similar proportion of patients receiving pdC1-INH liquid in crossover sequences and those receiving placebo experienced TEAEs (51.8% and 56.1%, respectively), treatment-related TEAEs (7.1% and 7.0%, respectively), and TEAEs within 24 hours after receiving study drug (12.5% and 12.3%, respectively). AE-related withdrawals are described above.

The TEAE profile was generally similar for pdC1-INH liquid and placebo (Table III). Commonly reported TEAEs by preferred term for pdC1-INH liquid crossover sequence groups included viral upper respiratory tract infection (12.5%), upper respiratory tract infection (12.5%), and headache (10.7%). Overall, no clinically meaningful changes from baseline occurred in mean biochemistry, hematology, coagulation parameters, or vital signs. No thromboembolic events, treatment-related SAEs, or deaths occurred.

Local tolerability. The incidence of ISRs was higher for patients receiving pdC1-INH liquid (59.2% in the overall group, 58.9% in the crossover groups) than placebo (26.3%). Erythema was the most commonly reported ISR, occurring more frequently with pdC1-INH liquid (56.3% in the overall group, 55.4% in the crossover groups) than placebo (22.8%). However, with both treatments, most reactions were mild, resolved within 12 hours, and rarely impacted daily living. No patients discontinued the study owing to the presence of ISRs.

Immunogenicity. No patients were positive for C1-INH antibodies before the first dose of study drug (ie, visit 1a), and no patients developed anti−C1-INH antibodies during the study.

PK and PD

Compared with placebo, functional C1-INH binding activity levels were higher in the treatment groups, regardless of whether placebo was administered before or after the active treatment. At treatment period 2, week 14 (visit 28b), mean exposure for functional C1-INH binding activity, plasma C1-INH antigen levels, and plasma complement C4 concentrations (described by AUC, C_{max}, and C_{min}) were notably higher in patients receiving pdC1-INH liquid than placebo, including minimum values of each exposure parameter (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Survey on patient experience with administration of pdC1-INH liquid

Most patients were satisfied/very satisfied with self-administration (59/64, 92%) and felt that the SC route was a better option than IV on a long-term basis (57/59, 97%). The majority of patients who previously received IV therapy for HAE reported preferring the SC route (43/49, 88%), and 81% (48/59) viewed the syringe as easy to use. Patients reported achieving self-administration with confidence within 1 to 2 study visits (mean [SD] 1.8 [1.7]), and all respondents (59/59) were able to self-administer without supervision.

DISCUSSION

Long-term prophylactic treatment against HAE attacks is a life-altering and potentially life-saving modality for many patients. Plasma-derived, IV-administered lyophilized C1-INH has historically been the standard of care for ongoing long-term prophylaxis. An SC ready-to-use liquid formulation may offer a more convenient treatment option. SAHARA is the first study to evaluate a fixed-dose, low-volume, SC-administered liquid C1-INH for prophylactic treatment against HAE attacks. Findings demonstrate that compared with placebo, treatment with pdC1-INH liquid SC led to significantly fewer attacks and fewer severe attacks, higher rates of responders, and higher number of attack-free days. pdC1-INH liquid has a favorable safety profile; no safety signals or trends were noted with respect to AEs, clinical laboratory results, vital signs, or immunogenicity.

Findings from this study add to previously published data evaluating pdC1-INH for the prophylactic treatment of HAE

attacks.[16,20] In the phase 3 randomized, double-blind, placebo-controlled crossover study evaluating patients with C1-INH-HAE, average normalized attack rates and attack severity were significantly lower and attack duration was significantly shorter with IV-administered C1-INH versus placebo.[16] In the phase 3 COMPACT study evaluating the SC-administered pdC1-INH, a weight-based dosing strategy provided significant attack rate reduction versus placebo.[20] Head-to-head studies evaluating long-term prophylactic treatments for C1-INH-HAE have not been conducted. Findings from our study help to build a continuum of improved patient care and experience.

Convenience of administration is an important aspect of patient compliance, especially for ongoing treatment; international treatment guidelines emphasize the need to consider patient preference when individualizing therapy.[8,13] A survey of 47 members of the US HAE Association evaluated patient experience with IV-administered C1-INH for on-demand treatment or prophylaxis.[22] The majority of participants (62%) who administered treatment using a peripheral vein reported at least occasional challenges related to accessing a vein or with the infusion itself, and almost half of participants (47%) using ports experienced difficulties, including infection and thrombosis.[22] In our study, findings from the patient experience survey show that pdC1-INH liquid was considered easy to self-administer. The majority of patients considered the SC route to be a better long-term option than the IV route. In addition, pdC1-INH liquid administration volume is low (4 mL; lower than required with weight-based C1-INH in most patients with HAE), and reconstitution is not required.

A limitation of this study is the fact that a crossover design may have a potential carryover effect. This was accounted for by several sensitivity analyses yielding consistent results (not shown) and by evaluating the findings starting from both day 1 and 15 of each treatment period.

CONCLUSIONS

Our findings demonstrate that twice-weekly, fixed-dose, SC-administered pdC1-INH liquid is an effective, well-tolerated option for prophylactic treatment against HAE attacks. Given the heavy burden of illness associated with C1-INH-HAE, the convenience of a fixed-dose, low-volume, ready-to-use prophylactic treatment option may help improve the patient experience.

Acknowledgment

We thank Yi Wang, Senior Director, Clinical Pharmacology and Pharmacokinetics, Shire (a Takeda company), for providing content direction on the PK/PD findings reported herein.

SAHARA Study Investigators: Canada: P. Keith, W. Yang; Germany: M. Maurer, I. Martinez-Saguer; Hungary: H. Farkas; Israel: A. Reshef, S. Kivity; Romania: D. Moldovan; Spain: T. Caballero, M. Guilarte, M. D. Hernandez, M. T. González-Quevedo; United States: A. Banerji, J. Bernstein, A. Bewtra, T. Craig, S. Fineman, R. Gower, J. Jacobs, D. Johnston, J. Kashkin, H. H. Li, W. R. Lumry, M. Manning, D. McNeil, I. Melamed, N. Mumneh, T. Nickel, J. Panuto, D. Soteres, R. Tachdjian, J. Offenberger, J. Wedner.

REFERENCES

1. Suffritti C, Zanichelli A, Maggioni L, Bonanni E, Cugno M, Cicardi M. High-molecular-weight kininogen cleavage correlates with disease states in the bradykinin mediated angioedema due to hereditary C1-inhibitor deficiency. Clin Exp Allergy 2014;44:1503-14.
2. Aygoren-Pursun E, Magerl M, Maetzel A, Maurer M. Epidemiology of bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. Orphanet J Rare Dis 2018;13:73.
3. Kaplan AP, Joseph K. Pathogenesis of hereditary angioedema: the role of the bradykinin-forming cascade. Immunol Allergy Clin North Am 2017;37:513-25.
4. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy 2014;69:602-16.
5. Nzeako UC, Longhurst HJ. Many faces of angioedema: focus on the diagnosis and management of abdominal manifestations of hereditary angioedema. Eur J Gastroenterol Hepatol 2012;24:353-61.
6. Banerji A. The burden of illness in patients with hereditary angioedema. Ann Allergy Asthma Immunol 2013;111:329-36.
7. Caballero T, Maurer M, Longhurst HJ, Aberer W, Bouillet L, Fabien V. Triggers and prodromal symptoms of angioedema attacks in patients with hereditary angioedema. J Investig Allergol Clin Immunol 2016;26:383-6.
8. Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema. Clin Rev Allergy Immunol 2016;51:230-9.
9. Jindal NL, Harniman E, Prior N, Perez-Fernandez E, Caballero T, Betschel S. Hereditary angioedema: health-related quality of life in Canadian patients as measured by the SF-36. Allergy Asthma Clin Immunol 2017;13:4.
10. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010;31:407-14.
11. Banerji A, Li Y, Busse P, Riedl MA, Holtzman NS, Li HH, et al. Hereditary angioedema from the patient's perspective: a follow-up patient survey. Allergy Asthma Proc 2018;39:212-23.
12. Banerji A, Bas M, Bernstein JA, Boccon-Gibod I, Bova M, Dempster J, et al. Expert perspectives on hereditary angioedema: key areas for advancements in care across the patient journey. Allergy Rhinol (Providence) 2016;7:172-81.
13. Maurer M, Magerl M, Ansotegui I, Aygoren Pursun E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. Allergy 2018;73:1575-96.
14. Lyseng-Williamson KA. Nanofiltered human C1 inhibitor concentrate (Cinryze®): in hereditary angioedema. BioDrugs 2011;25:317-27.
15. Farkas H, Varga L. Human plasma-derived, nanofiltered, C1-inhibitor concentrate (Cinryze®), a novel therapeutic alternative for the management of hereditary angioedema resulting from C1-inhibitor deficiency. Biol Ther 2012;2:2.
16. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 2010;363:513-22.
17. Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. Am J Med 2012;125:938.e1-7.
18. Cinryze [package insert]. Lexington, MA: Shire; 2018.
19. Chen M, Riedl MA. Emerging therapies in hereditary angioedema. Immunol Allergy Clin North Am 2017;37:585-95.
20. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. N Engl J Med 2017;376:1131-40.
21. Haegarda [package insert]. Marburg, Germany: CSL Behring GmbH; 2017.
22. Riedl MA, Banerji A, Busse PJ, Johnston DT, Davis-Lorton MA, Patel S, et al. Patient satisfaction and experience with intravenously administered C1-inhibitor concentrates in the United States. Ann Allergy Asthma Immunol 2017;119:59-64.

ONLINE REPOSITORY

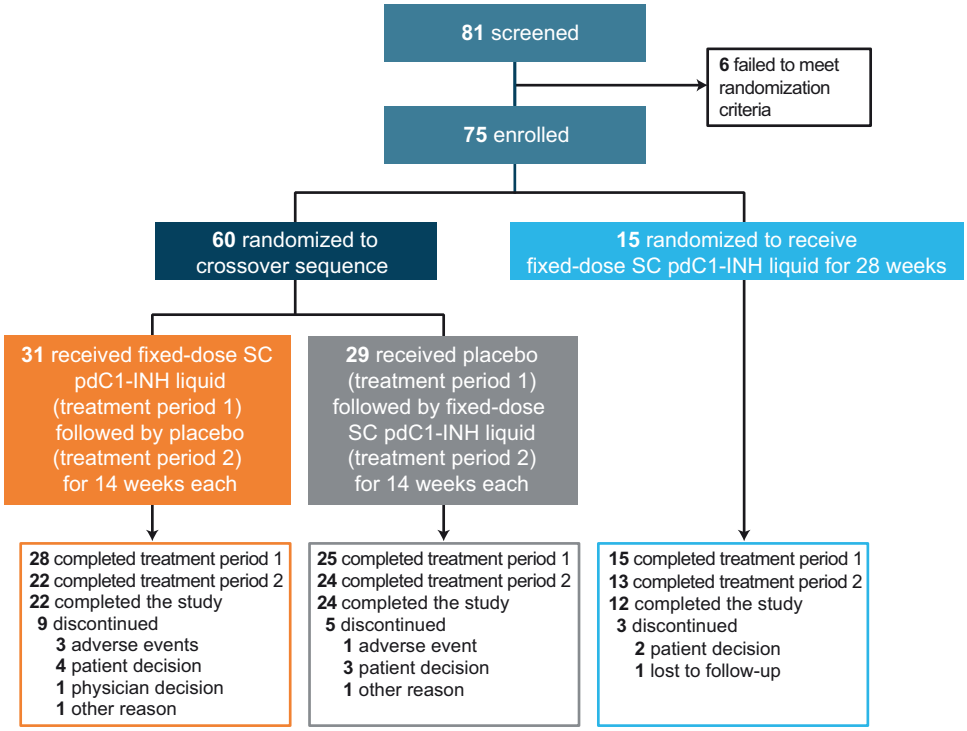

FIGURE E1. Patient disposition. One patient receiving pdC1-INH liquid experienced 2 TEAEs that led to treatment withdrawal (nausea and headache). Both events were considered treatment related and occurred within 24 hours of administration. Two patients receiving placebo experienced 2 TEAEs leading to withdrawal (one had cardiac arrest and the other had an HAE attack). Neither event was considered treatment related. *HAE*, Hereditary angioedema; *pdC1-INH*, plasma-derived C1-INH; *SC*, subcutaneous.

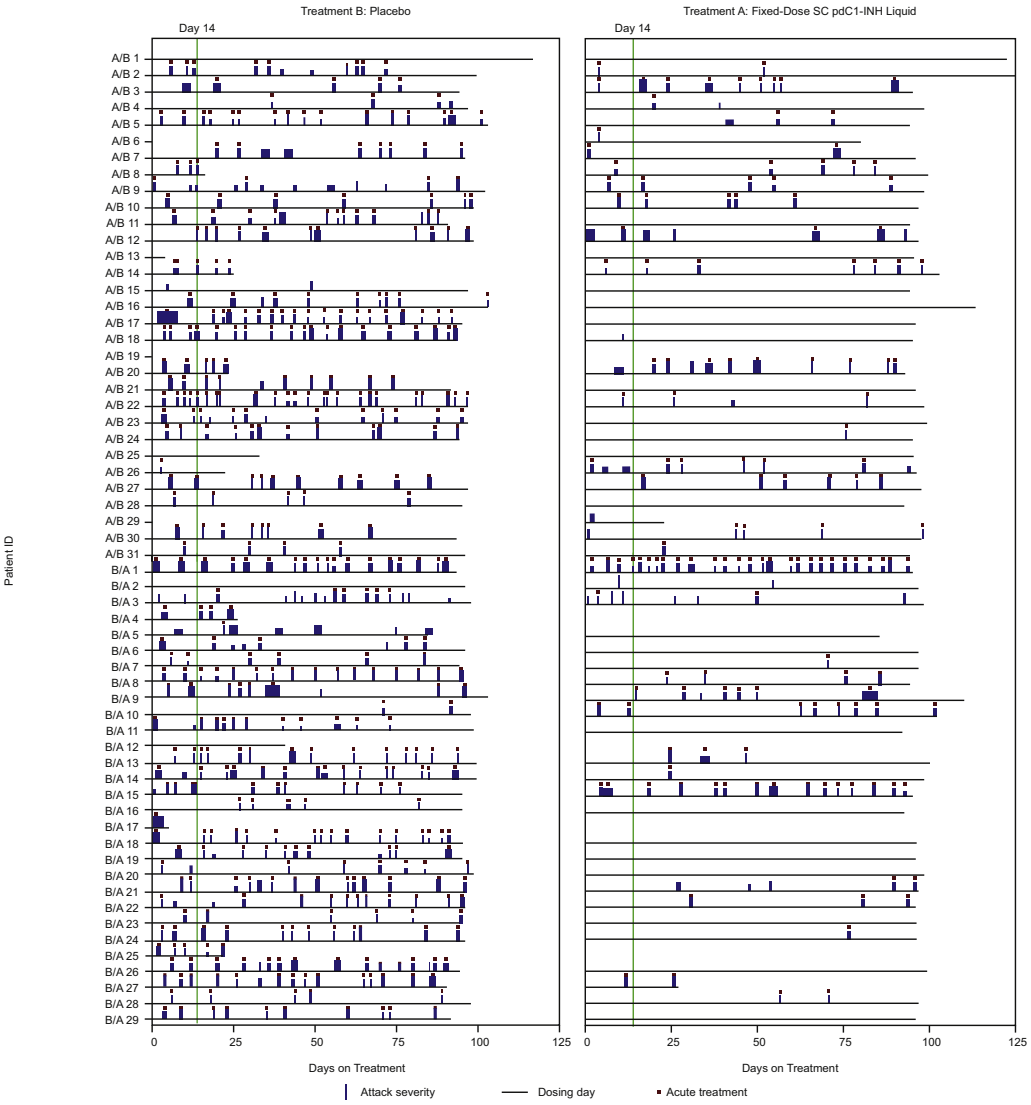

FIGURE E2. Occurrence of HAE attacks, attack severity, and use of on-demand medications. The height of vertical bars indicates the maximum attack severity of each dosing day, and the width indicates attack duration. The red dots indicate acute treatment. The horizontal lines indicate treatment duration. *HAE*, Hereditary angioedema.

TABLE E1. Blood sample collection times for PK/PD analyses

	Blood sampling time points*
Visit/Dose no.	**C1-INH antigen, C1-INH functional, C4**
Treatment period 1	
1a/Dose 1	Predose 1 (within 15 min)
2a/Dose 2†	Predose 2 (within 15 min)
8a/Dose 8	Predose 8 (within 15 min)
16a/Dose 16	Predose 16 (within 15 min)
24a/Dose 24	Predose 24 (within 15 min)
Either 27a or 28a/Dose 27 or 28‡	Predose 27 or 28 (within 15 min) 48 h after dose 27 or 28 (±3 h)
Treatment period 2	
1b/Dose 1	Predose 1 (within 15 min)
2b/Dose 2†	Predose 2 (within 15 min)
8b/Dose 8	Predose 8 (within 15 min)
16b/Dose 16	Predose 16 (within 15 min)
24b/Dose 24	Predose 24 (within 15 min)
28b/Dose 28	Predose 28 (within 15 min) 24 h after dose 28 (±3 h)—optional sampling time point 48 h after dose 28 (±3 h) 72 h after dose 28 (±6 h)—optional sampling time point 96 h after dose 28 (±6 h)
Early discontinuation (if applicable) and after treatment	
Early discontinuation	
1 wk (±1 d)	
1 mo (±2 d)	

C1-INH, C1 inhibitor; *PD*, pharmacodynamics; *PK*, pharmacokinetics.
*The actual date and time of each sample collection were recorded; therefore, the sampling window is provided for guidance as an approximate value.
†Subjects who self-administered investigational product without supervision were not required to have a blood sample collected at visit 2a or 2b.
‡To avoid collecting a PK/PD blood sample during the weekend, subjects had the option for a predose and a 48-hour postdose sample collected at either visit 27a or 28a.

TABLE E2. PK/PD parameters of functional C1-INH binding activity, plasma C1-INH antigen levels, and plasma complement C4 concentration (visit 28 in period 2)

	$AUC_{0\text{-}t}$ (mU × h/mL)	$AUC_{0\text{-}96}$ (mU × h/mL)	C_{max} (mU/mL)	t_{max} (h)	C_{min} (mU/mL)
C1-INH binding activity					
pdC1-INH liquid					
N	6	6	6	6	6
Mean (SD)	31,190 (17,389)	31,070 (17,396)	396.20 (273.013)	31.597 (12.7038)	258.15 (138.232)
Median	28,300	28,000	313.0	23.90	257.5
Min	15,400	15,400	200.1	22.90	79.4
Max	63,200	63,200	932.2	48.45	488.1
Placebo					
N	3	3	3	3	3
Mean (SD)	13,860 (7268.3)	13,860 (7269.0)	159.50 (82.982)	55.689 (49.4851)	125.90 (62.329)
Median	11,600	11,600	128.1	72.45	99.4
Min	8030	8030	96.8	0.00	81.2
Max	22,000	22,000	253.6	94.62	197.1
	$AUC_{0\text{-}t}$ (mcg × h/mL)	$AUC_{0\text{-}96}$ (mcg × h/mL)	C_{max} (mcg/mL)	t_{max} (h)	C_{min} (mcg/mL)
C1-INH antigen					
pdC1-INH liquid					
N	6	6	6	6	6
Mean (SD)	6902 (4574.0)	6882 (4586.0)	77.680 (52.4375)	31.656 (24.6912)	65.562 (45.9331)
Median	5110	5050	55.57	23.90	45.84
Min	3970	3970	46.06	0.00	34.01
Max	15,900	15,900	181.22	71.57	154.42
Placebo					
N	3	3	3	3	3
Mean (SD)	1849 (426.09)	1849 (426.36)	21.257 (5.1647)	47.578 (47.3106)	17.913 (4.4316)
Median	1830	1830	22.61	48.12	18.57
Min	1440	1440	15.55	0.00	13.19
Max	2290	2290	25.61	94.62	21.98
	$AUC_{0\text{-}t}$ (mg × h/L)	$AUC_{0\text{-}96}$ (mg × h/L)	C_{max} (mg/L)	t_{max} (h)	C_{min} (mg/L)
C4 concentration					
pdC1-INH liquid					
N	5	5	5	5	5
Mean (SD)	16,780 (895.63)	16,690 (803.60)	200 (30.82)	33.417 (36.5183)	158 (13.04)
Median	17,000	17,000	200	22.92	160
Min	15,600	15,600	170	0.00	140
Max	17,700	17,500	250	72.60	170
Placebo*					
N	2	2	2	2	2
Patient A	8840	8840	120	94.62	82
Patient B	2150	2150	27	48.12	18

$AUC_{0\text{-}96}$, Area under the plasma concentration-time curve from time zero to last measurable concentration; *$AUC_{0\text{-}t}$*, area under the plasma concentration-time curve from time zero extrapolated to the end of the dosing interval tau, where tau is approximately 84 hours (ie, average of every 3 or 4 days); C_{max}, maximum observed plasma concentration; C_{min}, minimum observed plasma concentration; *PD*, pharmacodynamics; *pdC1-INH,* plasma-derived C1 esterase inhibitor; *PK*, pharmacokinetics; *SD*, standard deviation; t_{max}, time of maximum observed plasma concentration.

*For patients receiving placebo, the mean, median, min, and max C4 concentrations were not calculated.