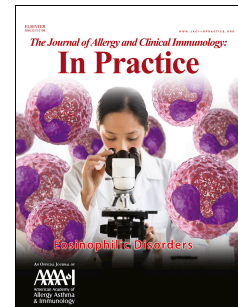


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Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks

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Title: Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks

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[†]Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT) investigators are provided in the in the Online Repository

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Conflict of Interest:

TC reports grant support from CSL Behring during the conduct of the study. He is a speaker for CSL Behring, Dyax, Grifols, Pharming and Shire. He reports grant support from Astra Zeneca, BioCryst, Boehringer Ingelheim, CSL Behring, Dyax, Genentech, GlaxoSmithKline, Grifols, Merck, Novartis, Pharming, Sanofi, and Shire. He has received consultancy fees and/or speaker's honoraria from BioCryst, Bellrose, CSL Behring, Dyax, Grifols, Merck, Novartis, Pharming Technologies and Shire. He has received travel support from CSL Behring, Pharming and Shire. He has received non-financial support from CSL Behring, Shire, and Grifols. BZ reports grant support from the Department of Defense, and

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Abstract

BACKGROUND: For the prevention of attacks of hereditary angioedema (HAE), the efficacy and safety of subcutaneous human C1-esterase inhibitor (C1-INH[SC]; HAEGARDA[®], CSL Behring) was established in the 16-week COMPACT trial.

OBJECTIVE: To assess the long-term safety, occurrence of angioedema attacks, and use of rescue medication with C1-INH(SC).

METHODS: Open-label, randomised, parallel-arm extension of COMPACT across 11 countries. Patients with frequent angioedema attacks, either study treatment-naïve or who had completed the COMPACT trial, were randomly assigned (1:1) to 40 IU/kg or 60 IU/kg C1-INH(SC) twice per week, with conditional up-titration to optimise prophylaxis. ClinicalTrials.gov registration: NCT02316353.

RESULTS: 126 patients with a monthly attack rate of 4.3 in 3 months prior to entry in the COMPACT program were enrolled and treated for a mean of 1.5 years; 44 patients (34.9%) had >2 years exposure. Median steady-state C1-INH functional activity increased to a maximum of 73.0% with 60 IU/kg. Incidence of adverse events was low and similar in both dose groups (11.3 and 8.5 events per patient-year for 40 IU/kg and 60 IU/kg, respectively). For 40 IU/kg and 60 IU/kg, median annualised attack rates were 1.3 and 1.0, respectively and median rescue medication use was 0.2 and 0.0 times per year, respectively. Of 23 patients receiving 60 IU/kg for >2 years, 19 (83%) were attack-free during months 25–30 of treatment.

CONCLUSION: In patients with frequent HAE attacks, long-term replacement therapy with C1-INH(SC) is safe and exhibits a substantial and sustained prophylactic effect, with the vast majority of patients becoming free from debilitating disease symptoms.

Highlights Box***What is already known about this topic?***

We searched PubMed for reviews discussing management of patients with hereditary angioedema (HAE). Twenty-one articles described barriers to long-term prophylaxis with intravenous human C1-esterase inhibitor (C1-INH) due to challenges with life-long vascular access and attack risk.

What does this article add to our knowledge?

The COMPACT long-term study demonstrates that continuous replacement therapy with subcutaneous C1-INH (C1-INH[SC]) provides sustained treatment effectiveness with minimal adverse effects.

How does this study impact current management guidelines?

This study confirms previous recommendations for C1-INH(SC) replacement as a safe and effective long-term prophylaxis against symptoms, attacks, and need for rescue therapy in HAE.

Key words: C1-esterase inhibitor protein, HAEGARDA, Hereditary angioedema, Subcutaneous, Long-term, Prophylaxis, Safety

Abbreviations:

AE, adverse event

C1-INH, C1 inhibitor

C1-INH(SC), subcutaneous human C1-esterase inhibitor

CI, confidence interval

HAE, hereditary angioedema

HRQoL, health-related quality of life

IPD, individual patient data

ITT, intention-to-treat

IU, international units

LLN, lower limit of normal

MI, myocardial infarction

ND, calculation not done

233 PK, pharmacokinetics
234 PD, pharmacodynamics
235 SAE, serious adverse event
236 SC, subcutaneously
237 SD, standard deviation
238 TP1, treatment period 1
239 TP2, treatment period 2

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INTRODUCTION

Hereditary angioedema (HAE), types I and II, is a rare autosomal dominant genetic disorder that results in a C1 inhibitor (C1-INH) protein deficiency or dysfunction.¹ It is a debilitating disease characterised by painful, disfiguring, and potentially fatal attacks of edema in the subcutaneous tissues of the face, trunk, and limbs, or the submucosal tissues of the upper respiratory, gastrointestinal, or genitourinary tracts.²⁻⁴

C1-INH is an endogenous multi-functional serine protease inhibitor (serpin) that is the major regulator of complement and contact system activation and is able to inactivate several fibrinolytic and coagulation system proteases.⁵ A major biological role of C1-INH is the regulation of vascular permeability by inhibition of the kallikrein-kinin system proteases, which mediate production of bradykinin.^{6, 7} C1-INH also suppresses inflammation via inhibition of the complement system and also suppresses the fibrinolytic system.⁶⁻⁸

Intravenous C1-INH replacement therapy has been used for many decades and is currently recommended as a first-line treatment of HAE and for the long-term prophylaxis of angioedema attacks.⁹ Routine prophylaxis with intravenous long-term C1-INH replacement therapy has been used since 2009, based on the outcomes of the CHANGE trial,¹⁰ but data from real-world clinical practice suggest that attacks can occur in about half of patients with HAE using intravenous C1-INH, and they often require higher doses than recommended in the product labelling, which also significantly increases cost.^{6, 11-13} Additionally, maintaining long-term venous access is challenging for many patients.⁹ Recently, a highly concentrated human plasma-derived C1-INH for subcutaneous injection (C1-INH[SC]; HAEGARDA®, CSL Behring; former investigational name CSL830) has been approved by regulatory agencies at a dose of 60 IU/kg twice weekly for long-term prophylaxis in patients with HAE, based on the COMPACT phase 3 randomised, double-blind, placebo-controlled crossover study.^{12, 14, 15} Both 40 IU/kg and 60 IU/kg doses of C1-INH(SC) administered twice per week significantly reduced the attack rate over the study period of 16 weeks. The higher dose of 60 IU/kg resulted in a median reduction in attacks versus placebo of 95%, as well as a reduction in

the use of rescue medications by a median of 100%.¹⁴ Both doses tested were efficacious and well tolerated, with the most commonly reported adverse events being mild injection-site reactions. In this publication, we describe the long-term, open-label extension of the COMPACT phase 3 study, which assessed the long-term safety and efficacy of 40 and 60 IU/kg of C1-INH(SC), each administered twice per week, for the prevention of angioedema attacks in patients with type I or II HAE.

METHODS

Study design

This study was a multicentre, randomised, parallel-arm, open-label extension of the phase 3 COMPACT study, performed in 32 hospitals across 11 countries (Australia, Canada, Czech Republic, Germany, Hungary, Israel, Italy, Romania, Spain, UK, and USA).

The study was done in accordance with the standards of Good Clinical Practice as defined by the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ethical principles that have their origin in the Declaration of Helsinki, and applicable national and local regulations. Study protocol and amendments were approved by independent ethics committees or institutional review boards at all participating centres prior to study commencement.

Patients

Patients who completed the COMPACT trial and study treatment-naïve patients were eligible to enrol into the COMPACT extension study to receive at least 52 weeks of continuous therapy with C1-INH(SC) 40 or 60 IU/kg twice per week.

Patients were eligible for the study if they were aged 6 years or older with a biochemically confirmed diagnosis of type I (C1-INH deficiency) or type II (C1-INH dysfunction) HAE, with C1-INH functional levels below 50%. Patients who had a history of experiencing frequent attacks (at least four attacks within 2 consecutive months) prior to

enrolment in to the COMPACT programme were eligible. Patients using oral prophylactic medication were required to be on a stable regimen and willing to continue this regimen for the study duration. Key exclusion criteria were any clinical conditions likely to interfere with the evaluation of the study drug, clinical history of poor response to C1-INH therapy, and any patient whose HAE could not be adequately managed by on-demand pharmacological treatment as assessed by the investigator. All patients, or their legal guardians, provided written informed consent.

Randomisation and masking

Patients either completed the placebo-controlled COMPACT trial or were study treatment-naïve on enrolment into the open-label extension study and were randomly assigned 1:1 to receive 40 or 60 IU/kg of C1-INH(SC) twice per week (concentration of 500 IU/ ml). C1-INH(SC) was administered as a single subcutaneous injection either independently (self-administered by the patient) or with assistance (with the help of a caregiver such as a parent or guardian). A stratified block randomisation scheme was used to ensure that participants were randomly assigned in a balanced manner. Participants were stratified by enrolment classification (study treatment-naïve, C1-INH-interrupted, or C1-INH-continuation) to ensure that patients in each of these categories were balanced between the treatment arms.

Procedures

The study included two treatment periods for all patients (Figure 1). Treatment period 1 constituted a 24-week fixed-dose treatment period, during which only patients experiencing 12 or more HAE attacks per 4-week evaluation period were eligible for incremental dose increases of 20 IU/kg up to a maximum dose of 80 IU/kg of subcutaneous C1-INH at the discretion of the investigator. Treatment period 2 was a 28-week dose-adjustment period wherein patients experiencing three or more attacks within an 8-week evaluation period were eligible for dose increases to optimise treatment response. A country-specific protocol

amendment (10 July, 2015) added an additional extension period to treatment period 2, which enabled patients from the USA to continue treatment, facilitating further long-term data collection for up to an additional 88 weeks. After the last visit in treatment period 2, the extension period or any visit resulting in study discontinuation, patients attended a follow-up assessment visit 2 weeks (± 3 days) later.

Blood samples were taken at the beginning, middle, and end of treatment periods 1 and 2 from patients for measurement of C1-INH functional activity, C1-INH antigen levels, and C4 antigen levels, and the patient data were summarised for each study group. C1-INH functional activity was assessed by a validated chromogenic assay (Berichrom C1-INH, Siemens, Marburg, Germany; normal range: 70–130% of the norm), and C1-INH and C4 protein levels were assessed by nephelometry (N Antiserum to Human C1-INH, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany; normal range: 0.18–0.32 mg/mL; C4 reagent, Beckman Coulter, Inc., Brea, CA, USA; normal range: 16–38 mg/dL).

Outcomes

The primary objective was to determine the long-term safety of C1-INH(SC). The primary pre-specified endpoints were person-time incidence rates of related serious adverse events, adverse events leading to premature discontinuation, adverse events of special interest (thromboembolic events and anaphylaxis), HAE attacks resulting in hospitalisation, injection-site reactions graded severe by the investigator, and the development of neutralising anti-C1-INH antibodies.

Secondary endpoints assessed additional safety parameters and efficacy of C1-INH(SC). Safety parameters included types of adverse events, suspected drug-related adverse events, and thromboembolic, anaphylaxis, sepsis, and bacteraemia events. Key efficacy endpoints included the percentage of patients with a time-normalised attack frequency of less than one attack per 4-week period, and the percentage of responders (defined as $\geq 50\%$ relative reduction in time-normalised number of attacks during treatment compared with the time-normalised number of attacks that was used to qualify the subject

for participation in this study). Further efficacy outcomes included time-normalised number of angioedema attacks, use of rescue medication, duration of attacks, and number of days when symptoms of HAE were experienced. The pharmacokinetics and pharmacodynamics (PK/PD) of treatment was an exploratory endpoint.

Statistical analysis

A sample size of 100 patients was planned to complete the study providing 95% confidence of observing one or more adverse events with a probability of 3%. Efficacy analyses were based on the intention-to-treat (ITT) population by the assigned dose at randomisation. The efficacy endpoints were summarised descriptively by treatment and overall. Safety and tolerability were monitored throughout the study, in addition to vital signs, weight, and laboratory parameters. Safety analyses were based on all patients in the safety population (all patients who were randomly assigned and received any study drug). Patients who were up-titrated from 40 IU/kg to 60 IU/kg were included in both treatments in the safety analysis. A Safety Data Monitoring and a Steering Committee provided scientific advice and safety monitoring for the study on an as-needed basis. This study was registered before enrolment of the first patient on ClinicalTrials.gov, number NCT02316353.

Role of the funding source

The sponsor of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the study report. All authors had full access to all the data in the study, approved the final published manuscript, and affirmed the integrity of the data and analyses. The corresponding author had final responsibility for the decision to submit for publication.

RESULTS

Between Dec 31, 2014, and May 17, 2016, 131 patients provided informed consent to participate in this extension study; 126 were randomly assigned to treatment and received at least one dose of study drug (safety population; Figure 1). All 126 patients were included in the ITT population. Both treatment groups comprised 63 patients each, with 32 (50.8%) patients previously treated with C1-INH(SC) in each group. Of the 126 patients in the study, 76 (60.3%) were female and 121 (96.0%) were Caucasian. The mean age was 40.5 years (standard deviation [SD] 15.6, range 8–72), with ten (7.9%) patients younger than 18 years old and three (2.4%) patients younger than 12 years old. Seven (11.1%) patients were up-titrated from 40 IU/kg to 60 IU/kg and were included in the safety population for both treatment groups. Of these, two (28.6%) patients were further up-titrated to 80 IU/kg. In addition, two (3.2%) patients randomly assigned to receive 60 IU/kg were up-titrated to 80 IU/kg during the extension period. Events recorded in the four (3.2%) patients up-titrated to 80 IU/kg were included in the ≥ 40 IU/kg analyses.

At database lock on Dec 20, 2017, 110 (87.3%) patients had completed the study. The baseline characteristics of the safety population are presented in table I. Before entry into either the COMPACT or COMPACT long-term safety study, the median pre-study 3-month attack rate was nine (60 IU/kg group) and ten (40 IU/kg group) attacks, respectively. Prophylactic treatment for HAE (either an attenuated androgen [$n=4$] or C1-INH replacement [$n=11$]) was used by eight of 35 (22.9%) and seven of 31 (22.6%) study treatment-naïve patients in the 60 IU/kg and 40 IU/kg groups, respectively. No notable differences were observed between the baseline characteristics of the 60 IU/kg and 40 IU/kg study groups.

Of the 15 (11.9%) patients who discontinued treatment before week 53, nine (7.1%) patients discontinued during treatment period 1 (four of 63 [6.3%] and five of 63 [7.9%] patients in the 60 IU/kg and 40 IU/kg groups, respectively), and six (4.8%) patients discontinued during treatment period 2 (three patients in each group). Additionally, one (1.6%) patient from the 60 IU/kg group discontinued during the extension period (Figure 1).

The duration of exposure in the safety population ranged from 2 to 140 weeks (median 52.6 weeks; mean [SD] 75.5 [39.5] weeks).

In total, 745 angioedema attacks were reported by 126 patients across both groups over an observation period of up to 2.7 years, resulting in median attack rates of 0.09 and 0.11 attacks per month (corresponding to 1.0 and 1.3 attacks per year) for patients in the 60 IU/kg and 40 IU/kg groups, respectively. 36 (57.1%) patients in the 60 IU/kg group and 31 (49.2%) patients in the 40 IU/kg group reported no or mild attacks, respectively. 17 (27.0%) patients in the 60 IU/kg group and 12 (19.0%) patients in the 40 IU/kg group reported at least one severe attack. In the 60 IU/kg group, 31 (49.2%) patients had an attack frequency of less than one attack per year compared with 27 (43.5%) patients in the 40 IU/kg group. 113 (92.6%) of 122 patients were defined as treatment responders (ie, $\geq 50\%$ reduction in the time-normalised number of HAE attacks; Table II). Up-titration by 20 IU/kg increments lowered the rate of attacks in seven (77.8%) of nine patients who continued to experience frequent attacks under their randomly assigned dose; the attack rate was unchanged in the remaining two patients.

61.7% (229 of 371 events) angioedema attacks were treated in the 60 IU/kg group and 51.3% (192 of 374 events) were treated in the 40 IU/kg group. Most patients with treated attacks were managed using a single rescue medication. 66.7% and 56.5% in the 60 IU/kg and 40 IU/kg groups, respectively, used less than one rescue medication per year. Post-hoc analysis of annualised rescue medication use showed that 39 (61.9%) patients receiving 60 IU/kg and 31 (50.0%) patients receiving 40 IU/kg used no rescue medication (Table II).

The median number of days with angioedema symptoms experienced per month was 0.12 and 0.18 days for the 60 IU/kg and 40 IU/kg treatment groups, respectively.

In a post-hoc analysis of 23 and 21 patients exposed to 60 IU/kg and 40 IU/kg C1-INH(SC), respectively, for more than 2 years, the percentage of patients who were completely attack-free within the last period of observation available for all patients (months 25–30) was numerically higher in the 60 IU/kg group than in the 40 IU/kg group (Figure 2A). In the 60 IU/kg dose group with more than 2 years' exposure, 19 (82.6%) of 23 patients were

completely attack-free and 20 (87.0%) of 23 patients did not use any rescue medication in months 25–30 of their observation period (Figure 2A and B).

Prior to prophylactic treatment, the mean (SD) C1-INH functional activity at baseline was 28.3% (8.0) and 30.4% (14.6) in the 60 IU/kg and 40 IU/kg treatment groups, respectively. The mean (SD) steady-state C1-INH functional activity increased with treatment to 66.6% (34.9) with 60 IU/kg and 52.0% (17.2) with 40 IU/kg at the end of study (Figure 3A and B). The mean (SD) concentration of C4 antigen at baseline was below normal levels,¹⁶ at 9.1 mg/dL (5.0) in the 60 IU/kg group and 10.5 mg/dL (5.4) in the 40 IU/kg group. The mean (SD) concentration of C4 antigen increased to close to normal levels with 60 IU/kg (16.3 mg/dL [6.6]) and to 14.8 mg/dL (5.9) with 40 IU/kg at the end of study (Figure 3C).

Similar adverse event profiles were reported in both treatment arms of the study, with an event rate of 8.5 and 11.3 adverse events per patient-year of exposure to 60 IU/kg and 40 IU/kg C1-INH(SC), respectively (Table III). The most frequently reported adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infections, headache, and localised injection-site reactions (see Table E1 in the Online Repository). No dose-dependent safety concerns were identified.

The most frequently observed adverse events were injection-site reactions. Overall incidence rates of injection-site reactions were 0.06 and 0.08 events per injection for 60 IU/kg and 40 IU/kg, respectively, but four patients, who were administered approximately 3% of all injections delivered during the study, accounted for more than 50.0% (675 of 1251 events) of all solicited adverse events. Most solicited adverse events occurred within 24 h after injection (1180 of 1251 events), were mild in severity (1234 of 1251 events), and were resolved within 24 h of appearance (955 of 1251 events). 12 serious adverse events were experienced by nine (7.1%) patients, one of which (myocardial infarction, unrelated to treatment) led to study discontinuation (details provided in footnote of Table III). Most serious adverse events were moderate or severe in intensity and resolved. None were deemed to be related to the study drug.

Four adverse events led to study discontinuation, including the unrelated serious adverse event of myocardial infarction. Four (3.2%) patients discontinued treatment due to pregnancy, having received a total exposure of 15–85 doses of C1-INH(SC), inclusive of administrations throughout the first trimester until pregnancy was detected. All women delivered healthy babies with no fetal abnormalities.

Aside from the single investigator-determined unrelated serious adverse event of myocardial infarction reported, no thromboembolic events were recorded during the study. No cases of anaphylaxis were reported. No neutralising antibodies to C1-INH were observed at baseline or at any post-baseline visit. No seropositive events for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus were recorded. No deaths occurred during the study period.

DISCUSSION

The COMPACT open-label extension study is the first and largest long-term study to investigate the safety and prophylactic effect of twice-weekly C1-INH(SC) over an extended period in patients with frequent HAE attacks, including children as young as 8 years old. Patients were exposed to C1-INH(SC) for a mean of 1.5 years; 23 patients were exposed to 60 IU/kg for over 2 years.

In this study, both doses of C1-INH(SC) were well tolerated and adverse events were infrequent and generally mild to moderate in intensity. The most common adverse effects were injection-site reactions related to the subcutaneous administration, a finding that is consistent with data from the placebo-controlled COMPACT study.¹⁴ The HAE patients studied were severely affected by their disease, and reported a median of ten attacks during the 3 months, and a mean of 4.3 attacks per month, prior to study entry, despite almost one quarter of study treatment-naïve patients already receiving a prophylaxis regimen. Over the course of the study, the median annualised attack rate was reduced to 1.0 attack per year and the percentage of patients achieving an attack rate of less than one attack per month

was 86% in the 60 IU/kg group. The majority of angioedema attacks experienced by patients in the study were mild to moderate. As anticipated, the use of rescue medication was very low, with a median annualised usage rate of 0.0 uses per year; 62.0% of patients did not use any rescue medication within 1 year in the 60 IU/kg treatment arm. Consistent with the placebo-controlled COMPACT trial,¹¹ the approved and recommended dosing of 60 IU/kg shows a numerically better prophylactic effect than the 40 IU/kg dose.¹⁴ This finding was evident as assessed by multiple efficacy endpoints, including the need for up-titration to the 60 IU/kg dose, which was necessary in seven (11.1%) of 63 patients in the 40 IU/kg arm, but only two (3.2%) of 63 patients required up-titration from the 60 IU/kg dose to 80 IU/kg.

C1-INH(SC) treatment resulted in a high number of attack-free patients by the end of the study. In patients treated for over 2 years with the 60 IU/kg dose, 20 (87.0%) of 23 patients no longer used any rescue medication, and 19 (82.6%) achieved an attack-free status in the month 25–30 observation period. There was no clinical evidence of tolerance induction or tachyphylaxis, as the proportion of attack-free patients increased over time. As seen in the pivotal COMPACT study,¹⁴ the 60 IU/kg dose achieved consistently higher C1-INH functional activity levels in patients, which were closer to the lower limit of normal and were more likely to normalise C4 protein levels than the 40 IU/kg dose. These data support previous findings of an inverse relationship of functional C1-INH activity levels and risk of an angioedema attack.¹⁷

HAE impairs health-related quality of life (HRQoL) through anxiety, loss of work productivity, and activity impairment. The unpredictability of angioedema attacks and the fear of asphyxiation make anxiety a particular burden.^{18, 19} Based on the COMPACT study,¹⁴ C1-INH(SC) improves several HRQoL impairments, particularly anxiety and work productivity, compared with on-demand treatment alone.¹⁸ Further explorations of the long-term HRQoL and health-economic impact with C1-INH(SC) will be the subject of ongoing research.

During the course of our study, four patients became pregnant and received treatment until the pregnancy was identified, treatment was discontinued according to protocol. All women delivered healthy babies. Human C1-INH is the only recommended

treatment for prophylaxis of angioedema attacks in pregnant or breastfeeding women.²⁰⁻²²

Because subcutaneous C1-INH only recently became available, clinical experience in special populations is sparse and further data in special populations may need to be collected. Nonetheless, the preparation of C1-INH used in this study is very similar to the preparation used for more than 30 years in the European Union, varying only in route of administration and concentration.

A limitation of this study is the inclusion of relatively low numbers of patients with specific co-morbidities and other circumstances that may affect the disease. HAE is often diagnosed in childhood and is present throughout a patient's lifetime, so although this long-term study extends the evidence base beyond the 16-week randomised study period, even longer-term evidence may need to be collected. Although paediatric and elderly patients participated in this study, the number of patients was small to examine any effects specific to these patient sub-groups. Furthermore, very rare treatment-related adverse events that may occur cannot be ruled out. In addition, the study could not fully address questions on the use of individualised dosing to optimize treatment response, since only few subjects had a dose up-titration and dose down-titration was not attempted.

In conclusion, this long-term extension study confirms previous results of the placebo-controlled COMPACT study¹⁴ and demonstrates durable efficacy with a sustained reduction in HAE attacks, symptoms, and the need for rescue medication. Long-term subcutaneous C1-INH replacement therapy provides a safe and sustained prophylactic treatment effect that allows patients to become free of HAE disease symptoms.

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Conference 2018 Scientific Meeting (May 17–20; Vienna, Austria).

Contributors

TC, BZ, HK, MC, KB, CG, HF, IP, DP, and IJ conceived and designed the study. CK, GS, PK, WY, JH, JH, PS, IM-S, MMag, EA-P, HF, AR, SK, S N, IC, TCa, MB, MD, HL, WL, JB, IH, JA, LBS, JJ, MMan, DL, MR, and SC acquired the data. All authors analysed and interpreted the data. TCa, HF, IP, and IJ wrote the first draft. All authors revised the manuscript for intellectual content. All authors approved the completed article.

Data sharing statement:

The sponsor of the study will consider requests to share Individual Patient Data (IPD) from review groups or bona-fide researchers. IPD requests will be accepted 12 months following publication on a public website. IPD will only be provided for the purposes of meta-analyses. The proposed use of the IPD will be reviewed by an internal CSL review committee.

If the request is approved and the researcher agrees to the terms and conditions, IPD that has been appropriately anonymized will be available. The IPD will then be available to the researcher for 2 years. Supporting documents including 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 IPD, please contact CSL Behring at clinicaltrials@csllbehring.com.

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FIGURE LEGENDS

FIGURE 1. Trial profile. Patient disposition for the trial and extension period. Arrows indicate up-titration of dose. *AE*, adverse event; *MI*, myocardial infarction; *TP1*, trial period 1; *TP2*, trial period 2; *IU*, international units.

FIGURE 2. Percentage of patients with over 2 years' exposure who were attack-free by 6-month time window (A) and who did not use any rescue medication (B), by 6-month time window.

FIGURE 3. Pharmacokinetic and pharmacodynamic findings over the course of the study. Mean (dots) and standard deviation (vertical lines) of C1-INH functional activity (A), C1-INH protein (B), and C4 protein (C). The grey boxed area indicates the extended study period. *LLN*, lower limit of normal (LLN taken from Tarzi et al.¹⁴).

TABLE I. Baseline characteristics (ITT population)

	C1-INH(SC) 40 IU/kg (N=63)	C1-INH(SC) 60 IU/kg (N=63)	C1-INH(SC) ≥40 IU/kg (N=126)
Age, years*			
Mean (SD)	40·8 (15·0)	40·3 (16·3)	40·5 (15·6)
Median (range)	43·0 (8–67)	41·0 (10–72)	41·0 (8–72)
Sex			
Women	40 (63%)	36 (57%)	76 (60%)
Men	23 (37%)	27 (43%)	50 (40%)
Race			
White	60 (95%)	61 (97%)	121 (96%)
Black or African American	1 (2%)	1 (2%)	2 (2%)
Asian	0	1 (2%)	1 (1%)
Other	2 (3%)	0 (0%)	2 (2%)
HAE type			
Type I	55 (87%)	58 (92%)	113 (90%)
Type II	8 (13%)	5 (8%)	13 (10%)
HAE attacks in the 3 months before screening			
Mean (SD)	12·8 (8·4)	12·7 (10·2)	12·8 (9·3)
Median (range)	10·0 (3–37)	9·0 (0–45)	10·0 (0–45)
Use of prophylaxis in the 3 months before screening[†]			
Overall	7 (23%)	8 (23%)	15 (24%)
C1-INH	6	5	11
Oral prophylaxis (danazol)	1	3	4

C1-INH, human plasma-derived C1-esterase inhibitor; HAE, hereditary angioedema; ITT, intention-to-treat; SC, subcutaneously; SD, standard deviation.

Data are n (%), mean (SD), or median (range).

*Ten patients were aged <18 years (range: 8–16 years, with three patients aged <12 years) and 10 patients were aged ≥65 years (range: 65–72 years).

[†]These data include only study treatment-naïve patients – 40 IU/kg (n=31), 60 IU/kg (n=35), ≥40 IU/kg (n=62).

TABLE II. Efficacy endpoints (ITT population)

	40 IU/kg (N=63)	60 IU/kg (N=63)	≥40 IU/kg (N=126)
Time-normalised attack rate			
Mean number of attacks/month (SD)	0.4 (0.7)	0.5 (0.9)	0.5 (0.8)
Median number attacks/month (range)	0.1 (0.0–3.4)	0.1 (0.0–4.0)	0.1 (0.0–4.0)
Mean number attacks/year (SD)	5.4 (8.8)	5.4 (10.3)	ND
Median number attacks/year (range)	1.3 (0.0–40.6)	1.0 (0.0–48.0)	ND
Time-normalised reduction to <1 attack per month			
<1 HAE attack/month, n (%)	50 (79%)	54 (86%)	104 (83%)
Time-normalised reduction in attack rate from baseline			
Mean (95% CI)	-6.8 (-9.8 to -3.8)	-6.8 (-10.9 to -2.7)	-6.8 (-9.3 to -4.3)
Responders (>50% reduction of attacks)			
n of responders/N with assessable data	58/62	55/60	113/122
Responder, % (95% Wilson CI)*	94% (85%–98%)	92% (82%–96%)	93% (87%–96%)
Time-normalised use of rescue medication			
Mean number medications/month (SD)	0.3 (0.6)	0.3 (0.8)	0.3 (0.7)
Median number medications/month (range)	0.02 (0.0–3.4)	0.0 (0.0–4.5)	0.0 (0.0–4.5)
Mean number medications/year (SD)	3.2 (6.9)	3.8 (9.6)	ND
Median number medications/year (range)	0.2 (0.0–40.6)	0.0 (0.0–54.2)	ND
Patients with minimal rescue medication use per year, n (%)			
<1 rescue medication/year	35 (57%)	42 (67%)	77 (62%)
No rescue medication/year	31 (50%)	39 (62%)	70 (56%)
Time-normalised number of days of angioedema symptoms per month			
Mean (SD)	1.3 (4.3)	0.7 (1.4)	1.0 (3.2)
Median (range)	0.2 (0.0–30.4)	0.1 (0.0–7.2)	0.1 (0.0–30.4)

C1-INH(SC), subcutaneously administered C1-esterase inhibitor; CI, confidence interval; HAE,

hereditary angioedema; ITT, intention-to-treat; ND, calculation not done; SD, standard deviation.

Data are n (%), mean (SD), or median (range), unless noted otherwise.

*The difference between C1-INH(SC) doses is assessed using Wilson asymptotic confidence limits for the difference in percentages.

TABLE III. Adverse events (safety population)

	40 IU/kg (N=63)		60 IU/kg (N=70)*		≥40 IU/kg (N=126)	
	n (%)	Events (events/patient-year)	n (%)	Events (events/patient-year)	n (%)	Events (events/patient-year)
AEs	56 (89)	948 (11·3)	58 (83)	849 (8·5)	108 (86)	1811 (9·7)
Mild	49 (78)	839 (10·0)	51 (73)	725 (7·3)	97 (77)	1572 (8·4)
Moderate	34 (54)	99 (1·2)	36 (51)	116 (1·2)	69 (55)	218 (1·2)
Severe	8 (13)	10 (0·1)	7 (10)	8 (0·1)	16 (13)	21 (0·11)
Treatment-related AEs	36 (57)	697 (8·3)	32 (46)	556 (5·6)	66 (52)	1257 (6·7)
AEs leading to discontinuation [†]	1 (2)	1 (0·0)	3 (4)	3 (0·0)	4 (3)	4 (0·0)
SAEs[‡]	4 (6)	5 (0·1)	5 (7)	6 (0·1)	9 (7)	12 (0·1)
Treatment-related SAEs	–	0	–	0	–	0
SAEs leading to discontinuation	–	0	1 (1)	1 (0·0)	1 (1)	1 (0·0)
Injection-site reactions[§]	35 (56)	692 (8·2)	32 (46)	554 (5·6)	65 (52)	1251 (6·7)
Unsolicited AEs	50 (79)	256 (3·1)	56 (80)	295 (3·0)	100 (79)	560 (3·0)
Treatment-related unsolicited AEs	4 (6)	5 (0·1)	3 (4)	4 (0·0)	7 (6)	9 (0·1)

AE, adverse event; SAE, serious adverse event.

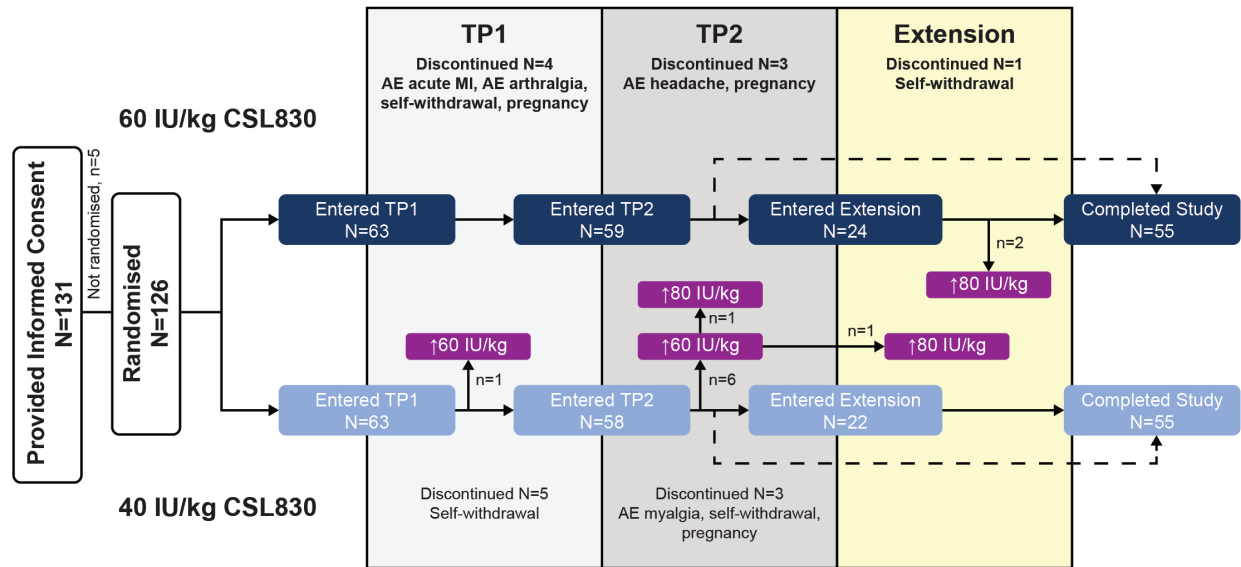
Data are n (%), unless noted otherwise.

*7 patients who were up-titrated from 40 IU/kg to 60 IU/kg were included in both treatment arms in the safety population. Therefore, the safety population included 63 subjects in the 40 IU/kg treatment and 70 subjects in the 60 IU/kg treatment.

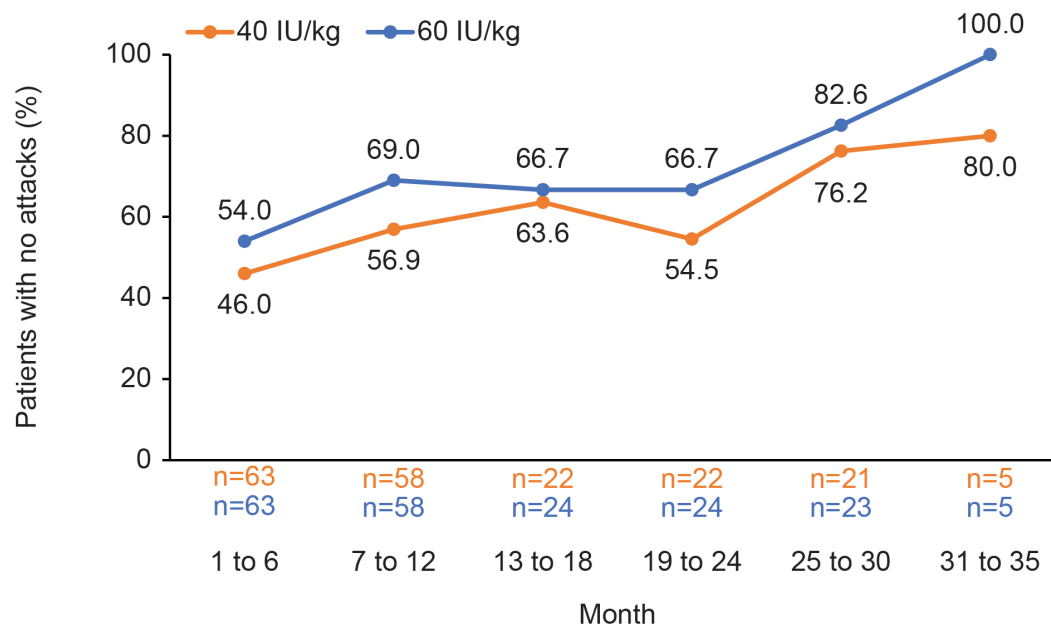
[†]Non-serious AEs leading to discontinuation were headache, myalgia and arthralgia.

[‡]Non-treatment-related SAEs were reported in nine patients (cholelithiasis, diffuse large B-cell lymphoma, contusion after fall, diplopia, acute myocardial infarction, hospitalisation due to dehydration and hypokalemia, dizziness and chest pain, bronchitis, pneumonia, and laryngeal attack resulting in hospital admission).

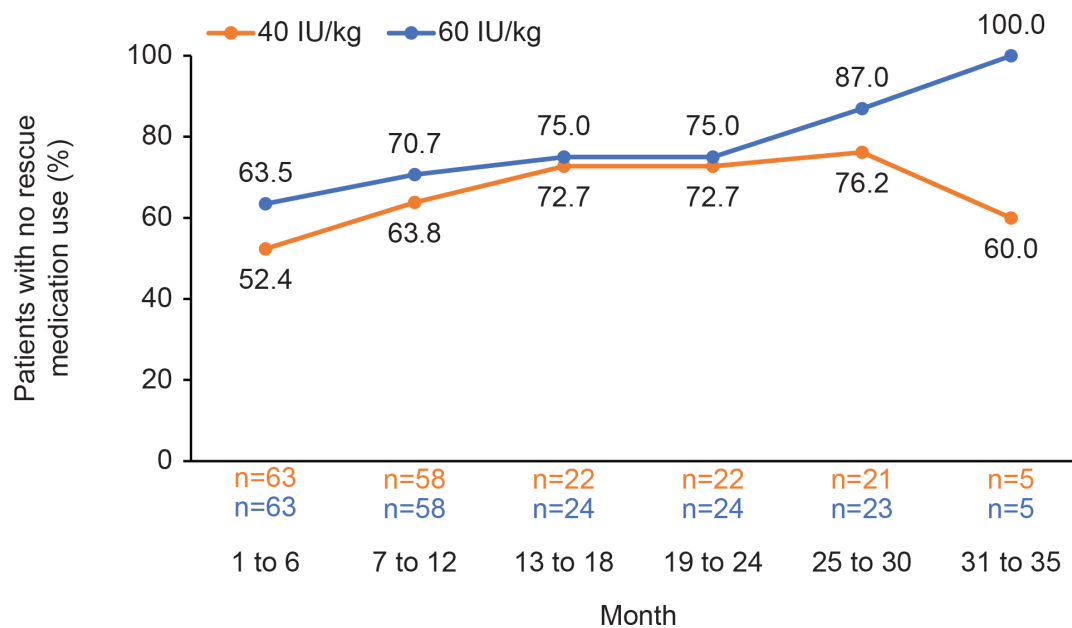
[§]Injection-site reactions included bruising, erythema, pain, swelling, edema, hemorrhage, and induration.



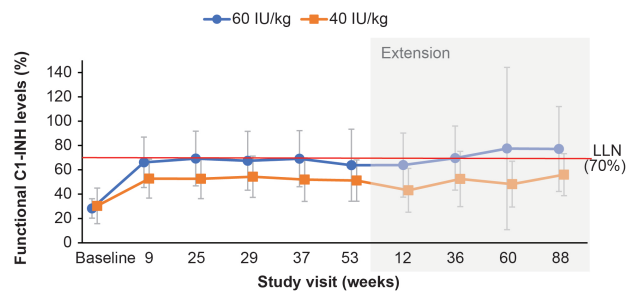
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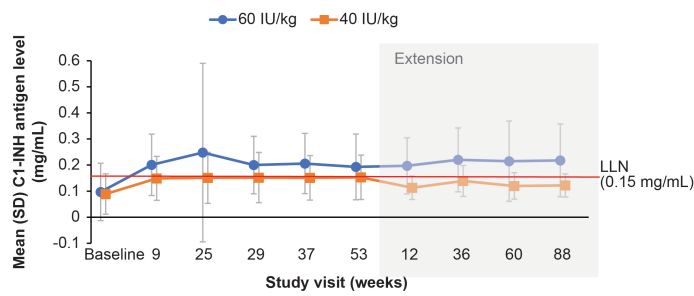
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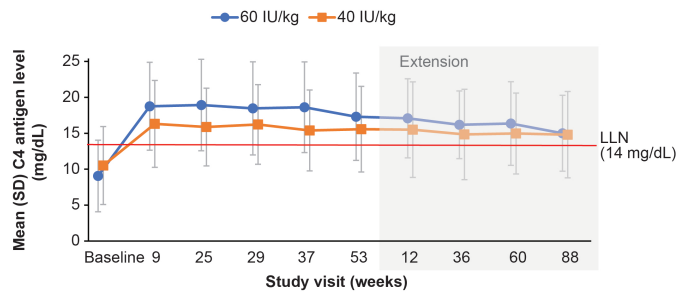
A)



B)



C)



Supplementary Appendix

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Central Clinical Laboratory: ACM Medical Laboratory, Rochester, US

Bioanalytical / Pharmacokinetic Analysis: CSL Behring GmbH, Marburg, Germany

Clinical Supply Service: Catalent Pharma Solutions, Schorndorf, Germany

Interactive Response Technology System: Perceptive eClinical Limited, Nottingham, UK

Data Management: Chiltern International GmbH, Bad Homburg, Germany

Electronic Diary: CRF Health, PA, US.

Safety Monitoring & Pharmacovigilance: CSL Behring GmbH, Marburg, Germany

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Supplementary Table: Adverse events reported in ≥5% of patients (safety population)

MedDRA preferred term	40 IU/kg (N=63)		60 IU/kg (N=70)		≥40 IU/kg (N=126)	
	n (%) [*]	Events (events/ exposure-year) [†]	n (%) [*]	Events (events/ exposure-year) [†]	n (%) [*]	Events (events/ exposure-year) [†]
Nasopharyngitis	12 (19.0)	23 (0.27)	21 (30.0)	36 (0.36)	32 (25.4)	61 (0.33)
Injection site pain	17 (27.0)	211 (2.52)	10 (14.3)	51 (0.51)	26 (20.6)	262 (1.40)
Injection site erythema	10 (15.9)	45 (0.54)	12 (17.1)	331 (3.32)	21 (16.7)	376 (2.01)
Headache	10 (15.9)	22 (0.26)	10 (14.3)	19 (0.19)	20 (15.9)	42 (0.22)
Injection site bruising	9 (14.3)	56 (0.67)	7 (10.0)	22 (0.22)	17 (13.5)	83 (0.44)
Upper respiratory tract infection	8 (12.7)	10 (0.12)	8 (11.4)	10 (0.10)	16 (12.7)	20 (0.11)
Injection site reaction	5 (7.9)	75 (0.89)	8 (11.4)	72 (0.72)	12 (9.5)	147 (0.79)
Arthralgia	6 (9.5)	6 (0.07)	5 (7.1)	5 (0.05)	11 (8.7)	11 (0.06)
Back pain	7 (11.1)	7 (0.08)	3 (4.3)	4 (0.04)	10 (7.9)	11 (0.06)
Bronchitis	7 (11.1)	7 (0.08)	2 (2.9)	2 (0.02)	9 (7.1)	9 (0.05)
Injection site hematoma	6 (9.5)	11 (0.13)	4 (5.7)	12 (0.12)	9 (7.1)	23 (0.12)
Nausea	5 (7.9)	10 (0.12)	4 (5.7)	14 (0.14)	9 (7.1)	24 (0.13)
Urinary tract infection	3 (4.8)	4 (0.05)	6 (8.6)	6 (0.06)	9 (7.1)	10 (0.05)
Sinusitis	4 (6.3)	4 (0.05)	4 (5.7)	7 (0.07)	8 (6.3)	11 (0.06)
Diarrhea	4 (6.3)	12 (0.14)	2 (2.9)	2 (0.02)	7 (5.6)	15 (0.08)
Injection site induration	4 (6.3)	19 (0.23)	3 (4.3)	4 (0.04)	7 (5.6)	23 (0.12)
Contusion	5 (7.9)	5 (0.06)	1 (1.4)	1 (0.01)	6 (4.8)	6 (0.03)
Injection site swelling	4 (6.3)	19 (0.23)	2 (2.9)	2 (0.02)	6 (4.8)	21 (0.11)
Myalgia	4 (6.3)	6 (0.07)	1 (1.4)	6 (0.06)	5 (4.0)	12 (0.06)
Toothache	1 (1.6)	1 (0.01)	4 (5.7)	4 (0.04)	5 (4.0)	5 (0.03)
Migraine	4 (6.3)	8 (0.10)	—	0 (0.00)	4 (3.2)	8 (0.04)

*Percentage of patients who experienced an adverse event (%) = (the number of patients with ≥ 1 event [n]) / (the number of patients receiving the corresponding treatment [N]). [†]Rate / Year = (the total number of events documented during the respective treatment) / (the total duration of exposure [in days] to the respective treatment) / (365.25 days).