

Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks



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What is already known about this topic? We searched PubMed for reviews discussing management of patients with hereditary angioedema. 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 long-term Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT) demonstrates that continuous replacement therapy with subcutaneous C1-INH provides sustained treatment effectiveness with minimal adverse effects.

How does this study impact current management guidelines? This study confirms previous recommendations for subcutaneous C1-INH replacement as a safe and effective long-term prophylaxis against symptoms, attacks, and need for rescue therapy in hereditary angioedema.

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 Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT).

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

METHODS: Open-label, randomized, parallel-arm extension of COMPACT across 11 countries. Patients with frequent angioedema attacks, either study treatment-naïve or who had completed COMPACT, were randomly assigned (1:1) to 40 IU/

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*Abbreviations used**C1-INH- C1 inhibitor**C1-INH(SC)- subcutaneous human C1-esterase inhibitor**COMPACT- Clinical Study for Optimal Management of**Preventing Angioedema with Low-Volume**Subcutaneous C1-Inhibitor Replacement Therapy**HAE- hereditary angioedema*

kg or 60 IU/kg C1-INH(SC) twice per week, with conditional upitration to optimize prophylaxis (ClinicalTrials.gov registration no. NCT02316353).

RESULTS: A total of 126 patients with a monthly attack rate of 4.3 in 3 months before entry in COMPACT were enrolled and treated for a mean of 1.5 years; 44 patients (34.9%) had more than 2 years of exposure. Mean steady-state C1-INH functional activity increased to 66.6% 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 annualized 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 more than 2 years, 19 (83%) were attack-free during months 25 to 30 of treatment.

CONCLUSIONS: 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. © 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-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2019;7:1793-802)

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

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 characterized 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

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Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT) investigators list is provided in this article's Online Repository at www.jaci-inpractice.org.

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at the Hereditary Angioedema Global Conference 2018 Scientific Meeting (May 17-20, Vienna, Austria).

This study was funded by CSL Behring. The sponsor of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the study report.

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 be provided only 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@cslbehring.com.

Conflicts of interest: T. Craig reports grant support from CSL Behring during the conduct of the study; is a speaker for CSL Behring, Dyax, Grifols, Pharming, and Shire; reports grant support from AstraZeneca, BioCryst, Boehringer Ingelheim, CSL Behring, Dyax, Genentech, GlaxoSmithKline, Grifols, Merck, Novartis, Pharming, Sanofi, and Shire; has received consultancy fees and/or speaker's honoraria from BioCryst, Bellrose, CSL Behring, Dyax, Grifols, Merck, Novartis, Pharming Technologies, and Shire; has received travel support from CSL Behring, Pharming, and Shire; and has received nonfinancial support from CSL Behring, Shire, and Grifols. B. Zuraw reports grant support from the Department of Defense; reports consultancy fees from Adverum, Alnylam, Arrowhead Pharmaceuticals, BioCryst, Nektar, CSL Behring, and Shire; and has led the Scientific Steering Committee for this study. H. Longhurst has received grant support, personal fees, and nonfinancial support from CSL Behring during the conduct of the study; grant support from BioCryst and Shire; personal fees from Adverum, BioCryst, Pharming, and Shire; and travel support from CSL Behring and nonfinancial support from Pharming and Shire. M. Cicardi has received grants from Shire and personal fees from Alnylam, BioCryst, CSL Behring, Dyax, KalVista, Pharming Technologies, Shire, Sobi (Swedish Orphan Biovitrum), and ViroPharma. K. Bork reports speaker fees from CSL Behring and Shire, outside the submitted work. C. Grattan reports personal fees as chair of the COMPACT Data Safety Monitoring Board (DSMB) from CSL Behring during the conduct of the study. C. Katelaris has received honoraria as a speaker and advisory board chair for Novartis, Shire, and Sequirus; has received travel support from Shire; and

C1-INH is an endogenous multifunctional 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.^{5,6} C1-INH also suppresses inflammation via inhibition of the complement system and also suppresses the fibrinolytic system.⁵⁻⁷

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.⁸ Routine prophylaxis with intravenous long-term C1-INH replacement therapy has been used since 2009, based on the outcomes of the CHANGE trial,⁹ but data from real-world clinical practice suggest that attacks can occur in about half the patients with HAE using intravenous C1-INH, and they often require higher doses than recommended in the product labeling, which also significantly increases cost.^{5,10-12} In addition, maintaining long-term venous access is challenging for many patients.⁸ Recently, a highly concentrated human

plasma-derived C1-INH for subcutaneous injection (C1-INH [SC]; HAEGARDA, CSL Behring, King of Prussia, Pa; 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 phase 3 randomized, double-blind, placebo-controlled crossover study titled Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT).^{11,13,14} 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 of 95% in attacks versus placebo, as well as a reduction in the use of rescue medications by a median of 100%.¹³ 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 phase 3 COMPACT, 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.

is a Principal Investigator for trials conducted by CSL Behring. G. Sussman has received grant support and personal fees from Novartis and personal fees from Merck, CSL Behring, and Pfizer, outside the submitted work. P. K. Keith has received grant support from CSL Behring and Shire during the conduct of the study, and consulting and speaker's honoraria from CSL Behring and Shire, outside the submitted work. W. Yang has served as an advisory board member for BioCryst Pharmaceuticals, CSL Behring, and Shire, and has received research and/or educational grants from BioCryst Pharmaceuticals, CSL Behring, Shire, and Pharming, outside of the submitted work. J. Hébert has been a Principal Investigator for CSL Behring clinical trials. P. Staubach-Renz has been a clinical trial investigator for CSL Behring and has received grants and/or speaker/consultant fees from AbbVie, Astellas, Celgene, CSL Behring, Genentech, Janssen, Karrer, LEO, Leti, Lilly, MSD, Novartis, Pfizer, Shire, Sobi (Swedish Orphan Biovitrum), UCB, and ViroPharma, outside the submitted work. I. Martinez-Saguer has received grants and speaker/consultant fees and been a clinical trial investigator for BioCryst, CSL Behring, Sobi (Swedish Orphan Biovitrum), Shire, and ViroPharma. M. Magerl has received financial compensation from CSL Behring for the conduct of the study and has also received speaker/consultant fees from BioCryst, CSL Behring, Novartis, Shire, and Pharming Technologies. E. Aygören-Pürsün has received grant support as a clinical trial investigator for this study and has received honoraria as a speaker/advisor and/or grant support/clinical trial investigator support from BioCryst, CSL Behring, KalVista, Pharming Technologies, Shire, and ViroPharma. H. Farkas received institutional support for a clinical trial for this study from CSL Behring; advisory board/consultancy fees and/or speaker's honoraria from BioCryst, CSL Behring, Shire, and Sobi (Swedish Orphan Biovitrum); and travel support from CSL Behring. S. Neri reports educational grants and honoraria for advisory boards and symposia from CSL Behring, Shire, and ViroPharma and other support from Pharming, outside of the submitted work. A. Reshef reports grant support from CSL Behring during the conduct of the study and has received grant support from Pharming. I. Crisan reports institutional support from CSL Behring during the conduct of the study. T. Caballero reports institutional support from CSL Behring during the conduct of the study; personal fees from BioCryst, CSL Behring, GlaxoSmithKline, MSD, and Sobi; personal fees and other support from CSL Behring, Novartis, and Shire HGT; and research funding from the IdiPaz Program for Promoting Research Activities, outside the submitted work. M. L. Baeza reports institutional support from CSL Behring during the conduct of the study. H. Li received institutional support from CSL Behring for the conduct of this study; travel expenses and/or consultancy fees and speaker's honoraria from BioCryst, CSL Behring, Shire, and Salix/Pharming; and institutional support for clinical trials from BioCryst, Pharming, and Shire. W. Lumry reports grant support from CSL Behring, Pharming, and Shire/Viropharma; consultancy fees/honorarium paid to his institution from Adverum, BioCryst Pharmaceuticals, CSL Behring, and Shire/Viropharma; travel support paid to his institution from CSL Behring and the US

Hereditary Angioedema Association; and fees for participation in review activities paid to his institution from BioCryst during the conduct of the study. J. A. Bernstein reports grant support and personal fees from BioCryst, CSL Behring, and Shire, outside the submitted work. I. Hussain reports institutional support from CSL Behring during the conduct of the study. J. Anderson reports personal fees as a consultant and for speaker's bureau participation from CSL Behring, Pharming, and Shire; and other clinical research support from BioCryst, CSL Behring, Dyax, and Shire, outside the submitted work. L. B. Schwartz reports grant support from CSL Behring during the conduct of the study and grant support from Dyax outside the submitted work. J. Jacobs reports grant support from CSL Behring during the conduct of the study; grant support from BioCryst, Dyax Corp, and Shire PLC; and honoraria and advisory fees from CSL Behring, Dyax Corp, Shire, Pharming, and Shire PLC, outside the submitted work. M. Manning reports grant support from BioCryst, CSL Behring, Dyax, and Shire; and personal fees from CSL Behring, Dyax, Pharming Technologies, Salix, and Shire, outside the submitted work. D. Levy has served on the speaker's bureau, as a consultant, on a steering committee, and as a clinical investigator for CSL Behring. M. Riedl reports grant support from CSL Behring during the conduct of the study and has received research grants from BioCryst, CSL Behring, Dyax, Ionis Pharmaceuticals, Pharming Technologies, and Shire; has served as a consultant and/or speaker for Adverum Biotechnologies, Alnylam Pharmaceuticals, Arrowhead Pharmaceuticals, BioCryst, CSL Behring, Dyax, Global Blood Therapeutics, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharming Technologies, Salix Pharmaceuticals, and Shire; and is an uncompensated advisory board member for the US Hereditary Angioedema Association, outside the submitted work. S. Christiansen reports receiving personal fees as an advisory board member from BioCryst, CSL Behring, and Shire, outside of the submitted work. H. Feuersenger, I. Pragst, S. Mycroft, D. Pawaskar, and I. Jacobs are employees of CSL Behring. I. Pragst has patents WO 2016/131958 A1 and WO 2018/037046 pending. D. Pawaskar has a patent pending. The rest of the authors declare that they have no relevant conflicts of interests.

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METHODS

Study design

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

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 centers before study commencement.

Patients

Patients who completed COMPACT and study treatment-naïve patients were eligible to enroll 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 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 4 attacks within 2 consecutive months) before enrollment into the COMPACT program 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.

Randomization and masking

Patients either completed the placebo-controlled COMPACT or were study treatment-naïve on enrollment 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 randomization scheme was used to ensure that participants were randomly assigned in a balanced manner. Participants were stratified by enrollment 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 2 treatment periods for all patients (Figure 1). Treatment period 1 constituted a 24-week fixed-dose treatment period, during which only those patients who were 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 C1-INH(SC) at the discretion of the investigator. Treatment period 2 was a 28-week dose-adjustment period wherein patients experiencing 3 or more attacks within an 8-week evaluation period were eligible for dose increases to optimize treatment

response. A country-specific protocol amendment (July 10, 2015) added an additional extension period to treatment period 2, which enabled patients from the United States 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 summarized 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, Calif; normal range, 16-38 mg/dL).

Outcomes

The primary objective was to determine the long-term safety of C1-INH(SC). The primary prespecified end points 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 hospitalization, injection-site reactions graded severe by the investigator, and the development of neutralizing anti-C1-INH antibodies.

Secondary end points 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 bacteremia events. Key efficacy end points included the percentage of patients with a time-normalized attack frequency of less than 1 attack per 4-week period, and the percentage of responders (defined as $\geq 50\%$ relative reduction in time-normalized number of attacks during treatment compared with the time-normalized number of attacks that was used to qualify the subject for participation in this study). Further efficacy outcomes included time-normalized 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 of treatment was an exploratory end point.

Statistical analysis

A sample size of 100 patients was planned to complete the study, providing 95% confidence of observing 1 or more adverse events with a probability of 3%. Efficacy analyses were based on the intention-to-treat population by the assigned dose at randomization. The efficacy end points were summarized 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 uptitrated from 40 IU/kg to 60 IU/kg were included in both treatments in the safety analysis. A Safety Data Monitoring Committee and a Steering Committee provided scientific advice and safety monitoring for the study on an as-needed basis. This study was registered before enrollment of the first patient on [ClinicalTrials.gov](https://clinicaltrials.gov) (no. NCT02316353).

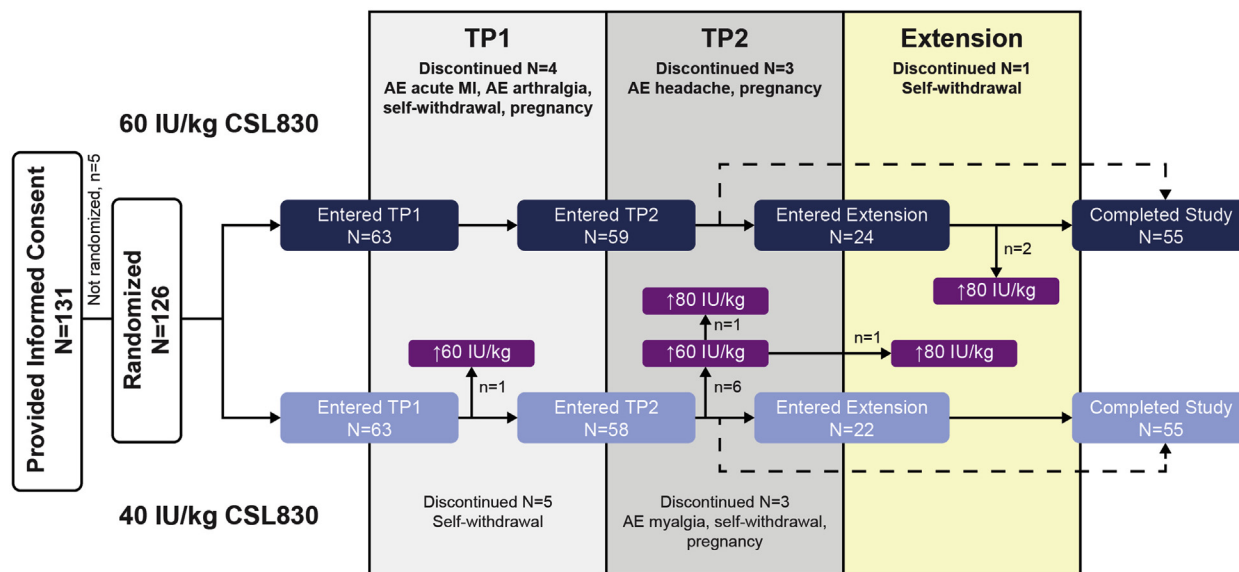


FIGURE 1. Trial profile. Patient disposition for the trial and extension periods. Arrows indicate uptitration of dose. *AE*, Adverse event; *MI*, myocardial infarction; *TP1*, trial period 1; *TP2*, trial period 2; *IU*, international units.

TABLE I. Baseline characteristics (ITT population)

Characteristic	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 (y)*			
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 mo 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 mo before screening†			
Overall	7 (23)	8 (23)	15 (24)
C1-INH	6	5	11
Oral prophylaxis (danazol)	1	3	4

ITT, Intention-to-treat.

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

*Ten patients were aged <18 y (range, 8-16 y, with 3 patients aged <12 y) and 10 patients were aged ≥65 y (range, 65-72 y).

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

RESULTS

Between December 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 1 dose of study drug (safety population; Figure 1). All 126 patients were included in the intention-to-treat 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 white. The mean age was 40.5 ± 15.6 years (range, 8-72 years), with 10 (7.9%) patients younger than 18 years and 3 (2.4%) patients younger than 12 years. Seven

TABLE II. Efficacy end points (ITT population)

Efficacy end points	40 IU/kg (N = 63)	60 IU/kg (N = 63)	≥40 IU/kg (N = 126)
Time-normalized attack rate			
No. of attacks/mo, mean ± SD	0.4 ± 0.7	0.5 ± 0.9	0.5 ± 0.8
Median no. of attacks/mo (range)	0.1 (0.0 to 3.4)	0.1 (0.0 to 4.0)	0.1 (0.0 to 4.0)
No. of attacks/y, mean ± SD	5.4 ± 8.8	5.4 ± 10.3	ND
Median no. of attacks/y (range)	1.3 (0.0 to 40.6)	1.0 (0.0 to 48.0)	ND
Time-normalized reduction to <1 attack per month			
<1 HAE attack/mo, n (%)	50 (79)	54 (86)	104 (83)
Time-normalized 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 in attacks)			
n of responders/N with assessable data	58/62	55/60	113/122
Responder, % (95% Wilson CI)*	94% (85% to 98%)	92% (82% to 96%)	93% (87% to 96%)
Time-normalized use of rescue medication			
No. of medications/mo, mean ± SD	0.3 ± 0.6	0.3 ± 0.8	0.3 ± 0.7
Median no. of medications/mo (range)	0.02 (0.0 to 3.4)	0.0 (0.0 to 4.5)	0.0 (0.0 to 4.5)
No. of medications/y, mean ± SD	3.2 ± 6.9	3.8 ± 9.6	ND
Median no. of medications/y (range)	0.2 (0.0 to 40.6)	0.0 (0.0 to 54.2)	ND
Patients with minimal rescue medication use per year, n (%)			
<1 rescue medication/y	35 (57)	42 (67)	77 (62)
No rescue medication/y	31 (50)	39 (62)	70 (56)
Time-normalized no. 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 to 30.4)	0.1 (0.0 to 7.2)	0.1 (0.0 to 30.4)

ITT, Intention-to-treat; ND, calculation not done.

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.

(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, 2 (28.6%) patients were further up-titrated to 80 IU/kg. In addition, 2 (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 4 (3.2%) patients up-titrated to 80 IU/kg were included in the greater than or equal to 40 IU/kg analyses.

At database lock on December 20, 2017, 110 (87.3%) patients had completed the study. The baseline characteristics of the safety population are presented in Table 1. Before entry into either COMPACT or COMPACT long-term safety, the median prestudy 3-month attack rate was 9 (60 IU/kg group) and 10 (40 IU/kg group) attacks, respectively. Prophylactic treatment for HAE (either attenuated androgen [n = 4] or C1-INH replacement [n = 11]) was used by 8 of 35 (22.9%) and 7 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, 9 (7.1%) patients discontinued during treatment period 1 (4 of 63 [6.3%] and 5 of 63 [7.9%] patients in the 60 IU/kg and 40 IU/kg groups, respectively) and 6 (4.8%) patients discontinued during treatment period 2 (3 patients in each group). In addition, 1 (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, 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. Thirty-six (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. Seventeen (27.0%) patients in the 60 IU/kg group and 12 (19.0%) patients in the 40 IU/kg group reported at least 1 severe attack. In the 60 IU/kg group, 31 (49.2%) patients had an attack frequency of less than 1 attack per year compared with 27 (43.5%) patients in the 40 IU/kg group. Out of 122 patients, 113 (92.6%) were defined as treatment responders (ie, ≥50% reduction in the time-normalized number of HAE attacks; Table II). Up-titration by 20 IU/kg increments lowered the rate of attacks in 7 (77.8%) of 9 patients who continued to experience frequent attacks under their randomly assigned dose; the attack rate was unchanged in the remaining 2 patients.

In the 60 IU/kg group, 61.7% (229 of 371 events) of angioedema attacks were treated, and in the 40 IU/kg group, 51.3% (192 of 374 events) of angioedema attacks were treated. Most patients with treated attacks were managed using a single rescue medication. In the 60 IU/kg and 40 IU/kg groups, 66.7% and 56.5%, respectively, used less than 1 rescue medication per year. Post hoc analysis of annualized rescue medication use showed

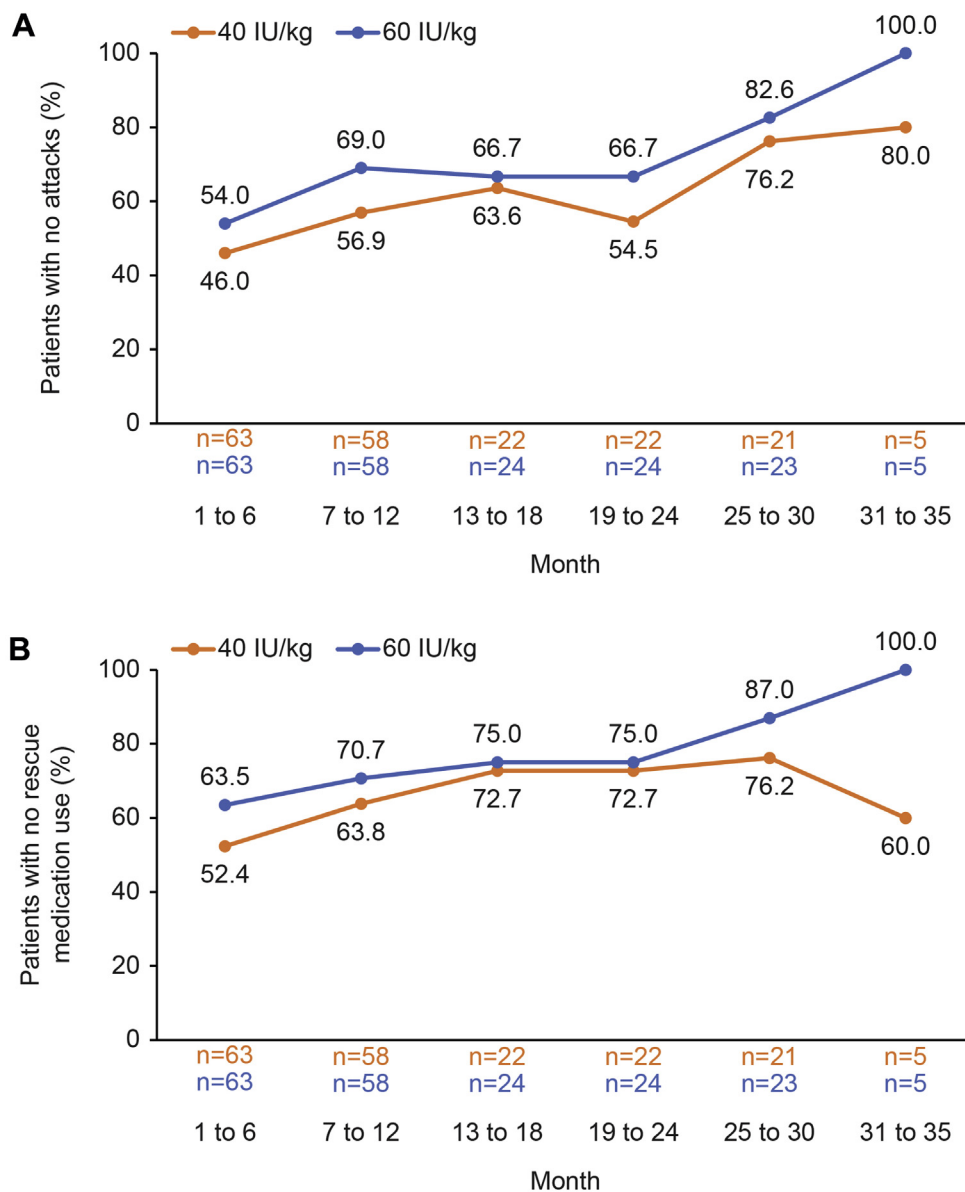


FIGURE 2. Percentage of patients with more than 2 years' exposure who were attack-free by 6-month time window (A) and who did not use any rescue medication (B), by 6-month time window. IU, International units.

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 day 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 2, A). 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 to 30 of their observation period (Figure 2, A and B).

Before prophylactic treatment, the mean C1-INH functional activity at baseline was $28.3\% \pm 8.0\%$ and $30.4\% \pm 14.6\%$ in the 60 IU/kg and 40 IU/kg treatment groups, respectively. The mean steady-state C1-INH functional activity increased with treatment to $66.6\% \pm 34.9\%$ with 60 IU/kg and $52.0\% \pm 17.2\%$ with 40 IU/kg at the end of study (Figure 3, A and B). The mean concentration of C4 antigen at baseline was below normal levels,¹⁵ at 9.1 ± 5.0 mg/dL in the 60 IU/kg group and 10.5 ± 5.4 mg/dL in the 40 IU/kg group. The mean concentration of C4 antigen increased to close to normal levels with 60 IU/kg (16.3 ± 6.6 mg/dL) and to 14.8 ± 5.9 mg/dL with 40 IU/kg at the end of the study (Figure 3, C).

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-

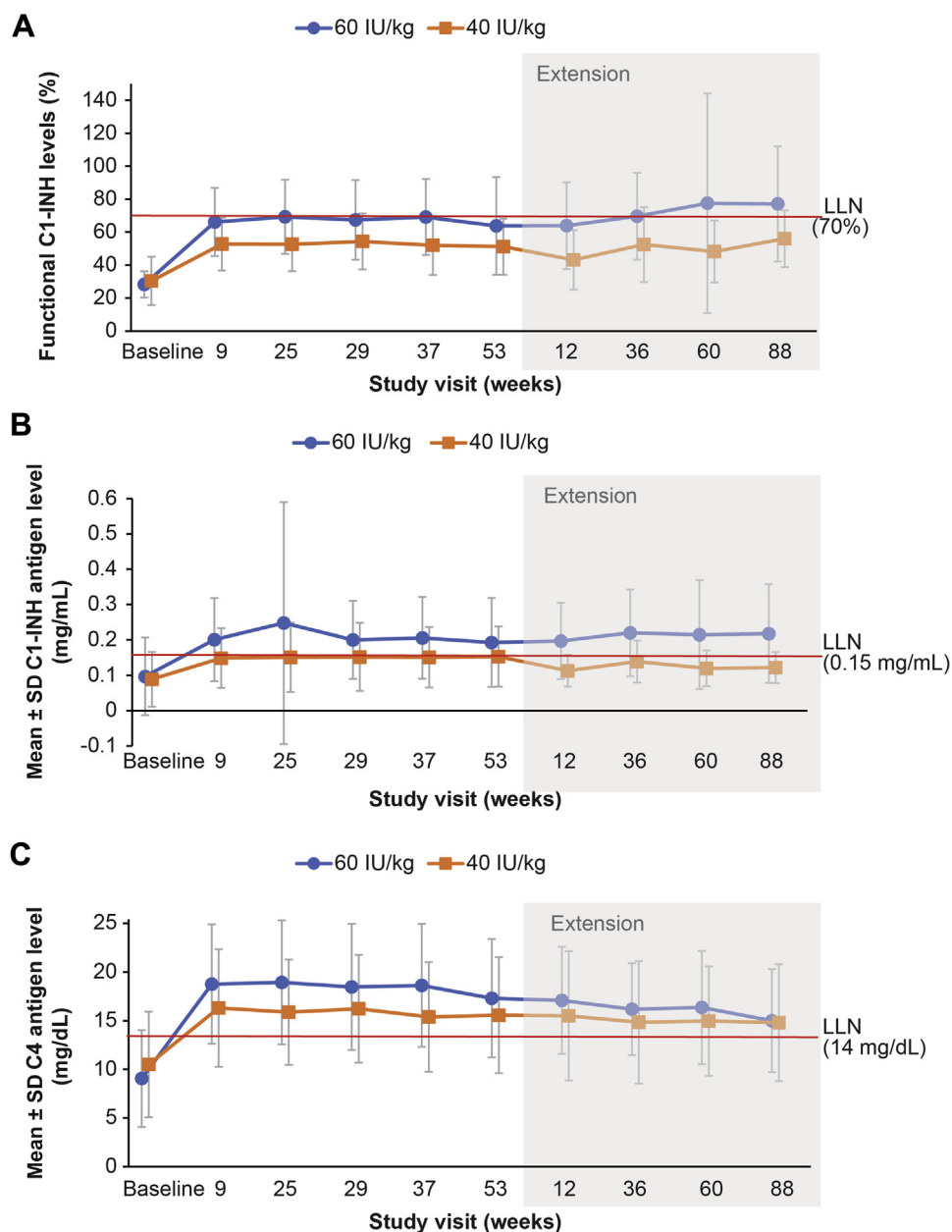


FIGURE 3. Pharmacokinetic and pharmacodynamic findings over the course of the study. Mean (dots) and SD (vertical lines) of C1-INH functional activity (A), C1-INH protein (B), and C4 protein (C). The gray boxed area indicates the extended study period. LLN, Lower limit of normal (LLN taken from Tarzi et al¹⁵). IU, International units.

INH(SC), respectively (Table III). The most frequently reported adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infections, headache, and localized injection-site reactions (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). 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 4 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 hours after injection (1180 of 1251 events), were mild in severity (1234 of 1251 events), and were resolved within 24 hours of appearance (955 of 1251 events).

Twelve serious adverse events were experienced by 9 (7.1%) patients, 1 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 was 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

TABLE III. AEs (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.

*Seven patients who were uptitrated 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 arm and 70 subjects in the 60 IU/kg treatment arm.

†Nonserious AEs leading to discontinuation were headache, myalgia, and arthralgia.

‡Nontreatment-related SAEs were reported in 9 patients (cholelithiasis, diffuse large B-cell lymphoma, contusion after fall, diplopia, acute myocardial infarction, hospitalization 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.

(3.2%) patients discontinued treatment because of pregnancy, having received a total exposure of 15 to 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 neutralizing antibodies to C1-INH were observed at baseline or at any postbaseline visit. No seropositive events for HIV, hepatitis B virus, or hepatitis C virus were recorded. No deaths occurred during the study period.

DISCUSSION

The open-label extension COMPACT 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. Patients were exposed to C1-INH(SC) for a mean of 1.5 years; 23 patients were exposed to 60 IU/kg for more than 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.¹³ The patients with HAE studied were severely affected by their disease, and reported a median of 10 attacks during the 3 months, and a mean of 4.3 attacks per month, before study entry, despite almost one-quarter of study treatment-naive patients already receiving a prophylaxis regimen. Over the course of the study, the median annualized attack rate was reduced to 1.0 attack per year and the percentage of patients achieving an attack rate of less than 1 attack per month was 86% in the 60 IU/kg group. Most 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 annualized 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,¹⁰ the approved and recommended dosing of 60 IU/kg shows a numerically better prophylactic effect than does the 40 IU/kg dose.¹³ This finding was evident as assessed by multiple efficacy end points, including the need for uptitration to the 60 IU/kg dose, which was necessary in 7 (11.1%) of 63 patients in the 40 IU/kg arm, but only 2 (3.2%) of 63 patients required uptitration 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 more than 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 observation period from month 25 to 30. 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,¹³ 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 normalize 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.¹⁶

HAE impairs health-related quality of life through anxiety, loss of work productivity, and activity impairment. The unpredictability of angioedema attacks and the fear of asphyxiation make anxiety a particular burden.^{17,18} On the basis of COMPACT,¹³ we can say that C1-INH(SC) improves several health-related quality-of-life impairments, particularly anxiety and work productivity, compared with on-demand treatment alone.¹⁷ Further explorations of the long-term health-related

quality of life and health-economic impact with C1-INH(SC) will be the subject of ongoing research.

During the course of our study, 4 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 breast-feeding women.¹⁹⁻²¹ Because C1-INH(SC) became available only recently, 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 comorbidities 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 randomized study period, even longer-term evidence may need to be collected. Although pediatric and elderly patients participated in this study, the number of patients was small to examine any effects specific to these patient subgroups. 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 individualized dosing to optimize treatment response, because 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 COMPACT¹³ 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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ONLINE REPOSITORY

APPENDIX

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TABLE E1. Adverse events reported in $\geq 5\%$ 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/y = (the total number of events documented during the respective treatment)/(the total duration of exposure [d] to the respective treatment)/(365.25 d).