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# Long-term safety and efficacy of subcutaneous C1-inhibitor in older patients with hereditary angioedema

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ABSTRACT

**Background:** Patients aged 65 years and older with hereditary angioedema (HAE) owing to C1-inhibitor (C1-INH) deficiency may have an altered response to treatment and are at higher risk for treatment-related adverse events (AEs) because of comorbidities and polypharmacy.
**Objective:** To investigate the safety and efficacy of subcutaneous C1 esterase inhibitor (C1-INH) in patients aged 65 years and older treated in an open-label extension of a phase 3 trial.
**Methods:** Eligible patients (≥4 attacks for more than 2 consecutive months) were randomized to receive twice-weekly subcutaneous C1-INH with a dosage of 40 IU/kg or 60 IU/kg for 52 to 140 weeks. Safety end points and efficacy outcomes were evaluated for patients aged 65 years and above and younger than 65 years.
**Results:** Of the 126 patients treated, 10 were 65 years and older (mean age [range], 68 [65-72 years]). A total of 8 of 10 patients had multiple comorbidities, and 6 of these 10 patients were taking more than 5 non–HAE-related drugs concomitantly. AEs occurring in more than 1 patient included injection site bruising (n = 2, related), injection site pain (n = 2, related), urinary tract infection (n = 2, unrelated), and diarrhea (n = 2, unrelated). No thromboembolic events or cases of anaphylaxis were reported. Two patients aged 65 years and older experienced unrelated serious AEs (dehydration and hypokalemia in 1 and pneumonia and an HAE

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attack leading to hospitalization in another). A total of 6 of 9 evaluable patients were responders, with a greater than or equal to 50% reduction in HAE attacks vs prestudy; 6 of 10 patients had less than 1 attack over 4 weeks and 3 were attack-free (median attack rate, 0.52 attacks per month).

**Conclusion:** Subcutaneous C1-INH was well-tolerated and effective in the management of HAE in patients aged 65 years and older with multiple comorbid conditions and polypharmacy.



## Introduction

Hereditary angioedema (HAE) owing to C1-esterase inhibitor (C1-INH) deficiency (C1-INH–HAE) is a rare autosomal-dominant disorder characterized by recurrent, debilitating attacks of non-pruritic bradykinin-mediated angioedema that typically affects the tissues of the face, trunk, extremities, and genitalia, and the upper airways and gastrointestinal tract.[1-3] The exact prevalence of C1-INH–HAE is unknown but has been estimated to be 1.5 per 100,000.[4] Symptoms usually commence in childhood, worsen around puberty, and persist throughout the patient's life.[3,5] HAE is associated with considerable morbidity and can be fatal if laryngeal angioedema is not managed promptly and appropriately, because it can lead to asphyxiation.[6,7] HAE attacks are unpredictable, making it difficult for patients to plan for travel or other life events, and often cause anxiety regarding future attacks.[8,9] In untreated patients, the frequency of attacks can range from a few attacks per year to 1 or more attacks per week.[1-3,10] Emotional stress, physical exertion, trauma, hormonal changes, and infection have been reported to trigger HAE attacks, but they can occur without any identifiable stimulus.[11,12]

The treatment of HAE in older adults (patients aged 65 years and older) presents several challenges. Age-related changes in physiology and pharmacokinetics (absorption, distribution, metabolism, and excretion) may affect the safety profile of a drug in older patients, putting them at higher risk for treatment-related adverse events (AEs).[13,14] Patients aged 65 years and older are more likely to have multiple comorbidities, leading to polypharmacy, which in turn may increase the likelihood of drug-related disease and drug-to-drug interactions.[14] The presence of comorbidities may also affect the clinical course of HAE, especially in women. In a retrospective study of 150 patients (mean age, 44.1 years; 16 patients aged 65 years and older), Martinez-Saguer et al[15] reported that the annual mean attack frequency was greater in patients with concomitant diseases, particularly in women (48.3 attacks per year in women with concomitant disease vs 28.6 attacks per year in women without concomitant disease). In the same study, the prevalence of comorbidities was higher in patients aged 65 years and older, as expected.

The 2017 World Allergy Organization guidelines for the management of HAE do not provide specific recommendations for older patients with HAE, but plasma-derived C1-INH (pdC1-INH) is cited as the preferred therapy for long-term prophylaxis in adult patients with C1-INH–HAE (types I or II).[16] Intravenously administered pdC1-INH has been available for prophylactic treatment of C1-INH–HAE for several years.[17,18] In June 2017, the first subcutaneous formulation of C1-INH (dose of 60 IU/kg, Haegarda, CSL Behring, Marburg, Germany) was approved by the United States Food and Drug Administration for routine prophylaxis to prevent HAE attacks among adolescents and adults.[18] The efficacy and safety of subcutaneous C1-INH has been reported in the pivotal, placebo-controlled phase 3 “Clinical study for Optimal Management of Preventing Angioedema with low-volume subcutaneous C1-Inhibitor Replacement Therapy” (COMPACT trial), and an open-label extension (OLE) of this trial, in which patients were treated for up to 2.7 years.[19,20] In the COMPACT trial, prophylaxis with subcutaneous C1-INH with a dose of 60 IU/kg twice-weekly resulted in a 95% median reduction in HAE attacks relative to placebo and a greater than 99% median reduction in rescue medication use.[19] In the OLE of this trial, the subcutaneous C1-INH doses of 40 IU/kg and 60 IU/kg had median annualized attack rates of 1.3 and 1.0 and annual median rescue medication use of 0.2 and 0.0 times per year, respectively.[20] In addition, the long-term prophylactic therapy with subcutaneous C1-INH was well-tolerated, with a low incidence of AEs (11.3 and 8.5 events per patient-year with subcutaneous C1-INH doses of 40 IU/kg and 60 IU/kg, respectively).[20]

In the current posthoc analysis, we evaluated the efficacy and safety of subcutaneous C1-INH in the subgroup of patients with C1-INH–HAE aged 65 years and older treated in the OLE of the COMPACT trial to determine whether older age and comorbidities might affect the efficacy and safety profile of subcutaneous C1-INH.

## Methods

The OLE of the COMPACT trial was a multicenter, randomized, parallel-arm study and included patients who had completed the placebo-controlled COMPACT trial in addition to subcutaneous C1-INH-naive patients. Eligible patients (age ≥6 years with ≥4 attacks more than 2 consecutive months before enrollment in the OLE or the COMPACT trial) were randomly assigned to receive subcutaneous C1-INH with a dose of either 40 IU/kg or 60 IU/kg twice-weekly for 52 weeks. Patients in the United States had the option to continue treatment for up to 140 weeks (Fig 1). The study included 2 treatment periods (TPs). During the first TP (24 weeks), 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 of 80 IU/kg at the discretion of the investigator. In the second TP (28 weeks), patients experiencing 3 or more attacks per 8-week evaluation period were eligible for dose increases to optimize treatment response.[20]

The primary objective of the OLE study was to assess the long-term safety of subcutaneous C1-INH.[20] The primary prespecified end points were the following: (1) person-time incidence rates of related serious AEs; (2) AEs leading to premature discontinuation; (3) AEs of special interest (thromboembolic events, anaphylaxis); (4) HAE attacks resulting in hospitalization; (5) injection site reactions graded as severe by the investigator; and (6) the development of anti–C1-INH antibodies.[20] Efficacy end points included the percentage of patients with less than 1 attack per 4-week period, and the percentage of responders (patients with ≥50% reduction in attacks relative to the prestudy period).[20]

In this posthoc analysis, the patients were analyzed by age subgroups (<65 years and ≥65 years at OLE study entry), based on the United States Food and Drug Administration definition of a geriatric population. Safety outcomes and the following efficacy end points were evaluated for these 2 age subgroups: (1) time-normalized number of HAE attacks, (2) percentage of responders, and (3) percentage of patients with less than 1 attack per 4-week period. Informed consent and Institutional Review Board review were not required for this study because existing data were utilized for posthoc analysis.

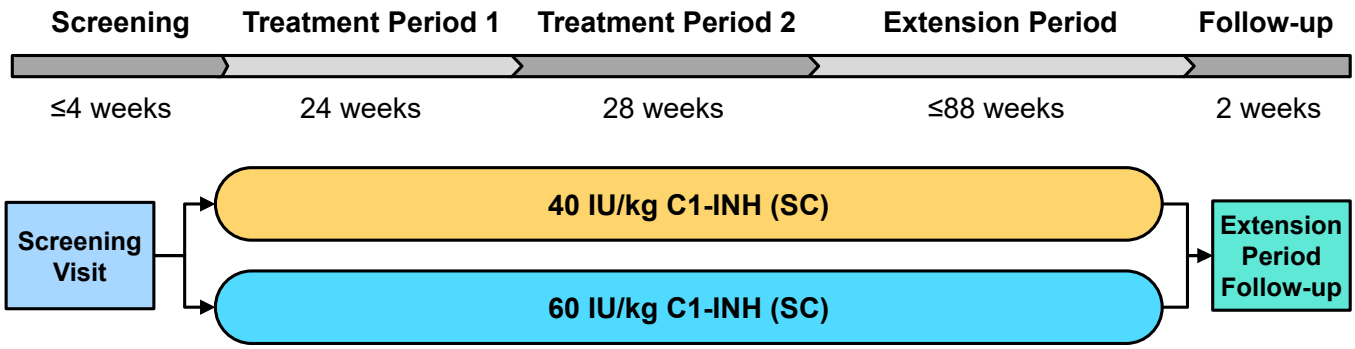


**Figure 1.** The study design of the clinical study for optimal management of preventing angioedema with low-volume subcutaneous C1-inhibitor replacement therapy open-label extension (COMPACT OLE trial). C1-INH, C1 esterase inhibitor; COMPACT, Clinical study for Optimal Management of Preventing Angioedema with low-volume subcutaneous C1-Inhibitor Replacement Therapy; OLE, open-label extension.

## Results

### *Baseline Demographics and Disease Characteristics*

Of the 126 patients randomized to treatment with subcutaneous C1-INH in the OLE of the COMPACT trial, 10 patients were aged 65 years and older (Table 1). The mean age in this older subgroup was 68 years (range, 65-72 years) and the mean (±SD) weight was 97.5 kg (±27.3 kg), substantially higher than the mean weight in patients less than 65 years old (84.1 ± 23.2 kg). The mean body mass index (BMI) was also higher in the older subgroup (33.8 kg/m$^2$ vs 28.8 kg/m$^2$). Notably, 8 of these patients had HAE type I, and 2 patients had HAE type II, consistent with the overall epidemiology of HAE.[1]

All 10 patients aged 65 years and older had at least 1 comorbidity, with the majority (8 of 10) having multiple comorbidities as follows: 8 had hypertension, 5 had diabetes mellitus, and 6 had hyperlipidemia, hypercholesterolemia or both. In addition, 4 patients had anxiety, depression disorders or both. Based on the World Health Organization definitions of overweight (BMI≥25 kg/m$^2$) and obesity (BMI≥30 kg/m$^2$),[21] all patients were overweight and 7 of 10 were obese. Consistent with the presence of multiple comorbidities in this older group, polypharmacy was common as well, with 6 patients taking more than 5 drugs for these comorbidities during the study (Table 2).

In patients aged 65 years and older treated with subcutaneous C1-INH, the median (range) duration of treatment in the efficacy evaluation period was 75 weeks (approximately 6-133 weeks). Two of the subcutaneous C1-INH–treated patients were randomized to the 40 IU/kg dose and 8 to the 60 IU/kg dose. Patients 3 and 6 had their dose uptitrated from 40 IU/kg and 60 IU/kg, respectively. Seven patients were previously enrolled in the placebo-controlled COMPACT trial and 3 were naive to subcutaneous C1-INH treatment.

No patients in the older subgroup discontinued because of an AE. One 68-year-old patient withdrew from the study after approximately 8 weeks because the "study was too much of a hassle." Another patient discontinued after approximately 2 years because of personal issues and a third withdrew after approximately 1 year (no reason was provided).

### *Safety Outcomes*

In the overall study population and in the subgroup of patients aged 65 years and older, subcutaneous C1-INH was well-tolerated. Local injection site reactions were the most common AEs and occurred in 5 patients. Specific AEs occurring in more than 1 patient in the subgroup aged 65 years and older included the following: (1) injection site bruising (n = 2, related); (2) injection site pain (n = 2, related); (3) urinary tract infection (n = 2, unrelated); and (4) diarrhea (n = 2, unrelated) (Table 3 and eTable 1).

In the overall population (N = 126), 12 serious AEs (all unrelated to treatment) occurred in 9 patients, 2 of whom belong to the subgroup aged 65 years and older. Patient 1, a 67-year-old woman, experienced dehydration and hypokalemia during treatment with the 40 IU/kg dose of subcutaneous C1-INH. The events resolved and did not lead to treatment discontinuation. Patient 6, a 68-year-old man, experienced pneumonia during treatment with the 60 IU/kg dose of subcutaneous C1-INH, and an HAE attack leading to hospitalization during treatment with the 80 IU/kg dose. Again, the events resolved and did not lead to treatment discontinuation. There were no treatment-related thromboembolic events or reports of anaphylaxis in any patients in both age subgroups.

### *Efficacy Outcomes*

Of the 9 patients in the older subgroup evaluable for the responder analysis, 6 were classified as responders, with a

**Table 1**
Baseline Demographic Characteristics by Age Group

| Characteristic | Patients <65 years old (n = 116) | Patients ≥65 years old (n = 10) |
|---|---|---|
| Age, y | | |
| Mean (SD) | 38.2 (13.9) | 67.9 (2.1) |
| Range | 8-64 | 65-72 |
| Female, % | 61.2 | 50 |
| Weight, kg, mean (SD) | 84.1 (23.2) | 97.5 (27.3) |
| BMI, kg/m$^2$, mean (SD) | 28.8 (7.2) | 33.8 (6.7) |
| Baseline attack rate before subcutaneous C1-INH treatment, mean (SD) | 4.4 (3.1) | 2.7 (2.5) |

Abbreviations: BMI, body mass index; C1-INH, C1 esterase inhibitor.

**Table 2**
Demographic and Disease Characteristics of Study Patients 65 Years Old and Above

| Patient | Sex | Age, y | BMI, kg/m$^2$ | Chronic comorbidities | Concomitant long-term medications |
|---|---|---|---|---|---|
| 1 | Female | 67 | 32.1 | CHF, depression, diarrhea, lower back pain, elevated creatinine, diastolic dysfunction, drug allergy/hypersensitivity, fibromyalgia, GERD, hypercholesterolemia, hypertension, hypothyroidism, iron deficiency, irritable bowel syndrome, T2DM, chronic UTIs, hypomagnesemia, lupus, dyspnea, leg cramps, nausea, edema, restless legs syndrome | Levothyroxine, SSRI, ondansetron, insulin, antipropulsive, gabapentin, iron, magnesium, PPI, hydroxychloroquine |
| 2 | Male | 68 | 30.3 | Anxiety, chronic pain, COPD, depression, hypercholesterolemia, intermittent constipation, hypertension, chronic insomnia, degenerative disk disease, retinal artery occlusion, chronically abnormal blood differential count | Albuterol, atenolol, duloxetine, fluticasone propionate/salmeterol, tiotropium bromide, lorazepam, simvastatin, trazodone |
| 3 | Female | 66 | 27.2 | Drug hypersensitivity, occasional arthralgias, allergic rhinitis | Cetirizine, fluticasone propionate |
| 4 | Male | 67 | 38.6 | Anxiety, depression, diarrhea, ED, chronic fatigue, chronic UTIs (related to prostate cancer), elevated GGT, hypercholesterolemia, hypertension, insomnia, allergic rhinitis, obstructive sleep apnea, T2DM | Verapamil, atorvastatin, liraglutide, glipizide, zolpidem tartrate, trazodone, amphetamine |
| 5 | Female | 71 | 25.2 | Diverticulitis, eczema, degenerative eye disease, GERD, stomach polyps, hypertension, degenerative disk disease | PPI, ranitidine, ipratropium bromide |
| 6 | Male | 68 | 39.2 | Hyperlipidemia, hypertension, obesity, osteoarthritis, T2DM | Metformin, glimepiride, insulin, carvedilol, valsartan, atorvastatin, canagliflozin |
| 7 | Male | 67 | 41.2 | Hypertension | Metoprolol, HCTZ |
| 8 | Female | 68 | 27.8 | Hypercholesterolemia, insomnia, allergic rhinitis, tachycardia | Zolpidem tartrate, metoprolol, rosuvastatin, ezetimibe, cetirizine |
| 9 | Female | 72 | 31.1 | Drug hypersensitivity/allergy, hypertension, hyperuricemia, hypokalemia, obesity, T2DM | Metoprolol, aspirin, insulin, HCTZ, sulfonamides, allopurinol, metformin, liraglutide, potassium |
| 10 | Male | 65 | 44.8 | Systolic ejection murmur, depression, diabetic neuropathy, ED, elevated GGT, hyperlipidemia, hypertension, obesity, allergic rhinitis, sleep apnea, T2DM | Losartan, glipizide, HCTZ, metformin, amlodipine, SSRI, pravastatin |

Abbreviations: BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ED, erectile dysfunction; GERD, gastroesophageal reflux disease; GGT, gamma-glutamyl transferase; HCTZ, hydrochlorothiazide; PPI, proton-pump inhibitor; SSRI, selective serotonin reuptake inhibitor; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

greater than or equal to 50% reduction in the time-normalized number of HAE attacks during treatment with subcutaneous C1-INH relative to the prestudy period (Table 4). Notably, 2 patients did not experience a decrease in attacks and 1 patient experienced a 42% reduction; 6 of 10 patients experienced less than 1 attack per 4-week period and 3 were attack-free. The mean number of HAE attacks per month decreased from 2.71 before the study to 0.86 with subcutaneous C1-INH. In comparison, among patients younger than 65 years old (n = 116), 106 (94%) of the 113 patients evaluable for the analysis were classified as responders, and 98 (85%) had less than 1 attack per week; 47 patients (40%) were attack-free. The mean number of HAE attacks per month decreased from 4.40 before the study to 0.42 with subcutaneous C1-INH.

The 3 nonresponding patients had multiple comorbidities, including hypertension, and were taking multiple concomitant medications. One nonresponder patient (patient 2) withdrew from the OLE after approximately 8 weeks (patient choice), experiencing 3 HAE attacks over the study evaluation period (Fig 2, first panel). The second nonresponder (patient 5) completed the OLE study and reported mostly mild and moderate attacks, with only 1 severe attack during the 1-year study period; of note, this patient's trough steady-state functional C1-INH level was above the reference range through most of the year of treatment (Fig 2, second panel). The third nonresponder, patient 6, reported mild to severe attacks, even when functional C1-INH levels were greater than 40% of normal (Fig 2, third panel); the frequency of attacks decreased when functional C1-INH levels increased to the lower limit of normal.

Patients 7, 8, and 10 (all treated with the 60 IU/kg dose) were attack-free during the treatment evaluation period, which ranged from approximately 1-2.6 years. A qualitative review of the demographic and disease characteristics of these patients did not reveal any predictive factors for an attack-free response. In the 3 attack-free patients, functional C1-INH levels were maintained above the 40% level proposed to have a prophylactic therapeutic effect at almost all time points (eTable 2).[22,23]

## Discussion

In this posthoc analysis of patients aged 65 years and above with C1-INH–HAE treated prophylactically with subcutaneous C1-INH in the OLE of the COMPACT trial, subcutaneous C1-INH was found to be generally safe and well-tolerated despite all patients having multiple comorbidities and polypharmacy. No patient in this subgroup discontinued because of an AE. In addition, subcutaneous C1-INH was effective, with 3 of 10 patients aged 65 years and older having no attacks for approximately 1-2.6 years and 6 of 10 having an average of less than 1 attack per month.

Studies of older adults with C1-INH–HAE are limited.[15,24,25] Older age may influence the clinical course of C1-INH–HAE and complicate the treatment owing to concurrent comorbidities and

**Table 3**
Adverse Event Profile of Subcutaneous C1 Esterase Inhibitor in Patients 65 Years Old and Above

| Adverse events | No. of patients (N = 10) | No. of events (no. of injections = 1605) |
|---|---|---|
| Treatment-related AEs | | |
| Injection site pain | 2 | 2 |
| Injection site hematoma | 1 | 1 |
| Injection site hemorrhage | 1 | 1 |
| Injection site induration | 1 | 1 |
| Injection site bruising | 2 | 3 |
| Serious AEs | | |
| Dehydration | 1 | 1 |
| Hypokalemia | 1 | 1 |
| Pneumonia | 1 | 1 |
| HAE leading to hospitalization | 1 | 1 |
| Unsolicited AEs occurring in >1 patient | | |
| Urinary tract infection | 2 | 3 |
| Diarrhea | 2 | 2 |

Abbreviations: AE, adverse event. HAE, hereditary angioedema.

their associated medications.[13-15] In patients aged 65 years and older treated in this study, hypertension was the most common comorbidity; type 2 diabetes mellitus and hypercholesterolemia were also frequently reported. These findings are consistent with other studies in similar HAE populations. In a retrospective study of older patients (≥65 years) with HAE, hypertension was the most common comorbidity.[24] In another retrospective HAE study comparing 134 patients younger than 65 years with 16 older patients, the most common comorbidities in the older cohort were arterial hypertension (62.5%), autoimmune thyroiditis (31.3%), allergic rhinitis (18.8%), and hypercholesterolemia (18.8%).[15] The prevalence of these comorbidities was higher in the older cohort. In the same study, the presence of comorbidities was associated with a higher frequency of attacks, especially in women.[15] In our study, all patients in the older subgroup had multiple comorbidities.

In the 2017 World Allergy Organization guidelines, pdC1-INH is cited as the preferred therapy for long-term prophylaxis in adult patients with C1-INH–HAE.[16] In the observational Berinert (C1 esterase inhibitor [human], CSL Behring, Marburg, Germany) patient registry, intravenous pdC1-INH therapy used for acute or prophylactic treatment was found to be safe in older adults with C1-INH–HAE, with low rates of AEs similar to younger adults.[25] The results of this posthoc analysis were consistent with the Berinert registry study[25] and indicated that the subcutaneous formulation of C1-INH is also well-tolerated and safe as a prophylactic treatment in adolescents and adults, including patients aged 65 years and older. The most common treatment-related AEs were 1-3 mild injection site reactions per patient, which occurred in 5 of 10 patients, each reaction resolving without further treatment.

Adverse events of special interest in the COMPACT OLE study included thromboembolic events and anaphylaxis events. Aging itself is a strong risk factor for thromboembolic disease, and diseases such as congestive heart failure, chronic obstructive pulmonary disease, and diabetes mellitus, which were observed in our older subgroup, are associated with an increased risk of thromboembolic events.[26] There were no thromboembolic events reported in this group of patients aged 65 years and older, despite the inherently increased risk in this age group. In addition, no case of anaphylaxis was reported in this older subgroup (or in the overall population) despite a history of drug hypersensitivity in 3 of the 10 patients aged 65 years and older.

As expected in a population with multiple comorbidities, polypharmacy was common in our subgroup of older patients, with 6 of 10 taking more than 5 drugs concomitantly. Because C1-INH replacement therapy is designed to correct an underlying deficiency using the human pdC1-INH protein, considerable drug interactions would not be expected with subcutaneous C1-INH prophylaxis. This may be an important consideration in older patients who are likely to be taking multiple medications concomitantly.

All patients in our older subgroup were overweight or obese and 5 of 10 had type 2 diabetes. Venous access may be difficult in patients with comorbidities, such as type 2 diabetes or obesity.[27] For such patients, subcutaneous C1-INH is a convenient alternative to intravenous C1-INH therapy and obviates the need for venous access.

In conclusion, the results of this posthoc analysis of the OLE of the COMPACT trial indicated that subcutaneous C1-INH provides an effective, safe, and well-tolerated long-term prophylaxis of angioedema attacks in patients aged 65 years and older with C1-INH–HAE despite multiple comorbidities and polypharmacy. Additional analyses using a broader definition of “older” adults (eg, ≥60 years or ≥55 years) are planned.

## Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2020.05.015.

**Table 4**
Efficacy Outcomes in Patients 65 Years Old and Above Treated Long-Term With Subcutaneous C1 Esterase Inhibitor

| Patient | Subcutaneous C1-INH treatment status | Subcutaneous C1-INH dose at randomization (IU/kg) | Evaluation period (weeks) during subcutaneous C1-INH exposure[a] | Responder (≥50% reduction in attacks vs prestudy) | <1 Attack/4-week Period |
|---|---|---|---|---|---|
| 1 | Previously treated | 40 | 48.7 | Yes | No |
| 2 | Previously treated | 60 | 6.1[b] | No | No |
| 3 | Previously treated | 40[c] | 117.4 | Yes | Yes |
| 4 | Previously treated | 60 | 99.1 | Yes | Yes |
| 5 | Previously treated | 60 | 50.4 | No | No |
| 6 | Previously treated | 60[c] | 133.4 | No | No |
| 7 | Naive | 60 | 116.1 | Yes (attack-free) | Yes (attack-free) |
| 8 | Naive | 60 | 50.1 | Yes (attack-free) | Yes (attack-free) |
| 9 | Naive | 60 | 50.4 | Yes | Yes |
| 10 | Previously treated | 60 | 127.1 | NE[d] (attack-free) | Yes (attack-free) |

Abbreviations: C1-INH, C1 esterase inhibitor; NE, not evaluable; SC, subcutaneous.
[a]The treatment evaluation period began at week 3 of treatment.
[b]Patient withdrew early from the study owing to personal reasons.
[c]Patient was uptitrated.
[d]Because of an investigator data entry error, the attack rate during intravenous C1-INH prophylaxis (0 attacks) was recorded as the prestudy attack rate. Therefore, a percent reduction in attacks could not be calculated for this patient.

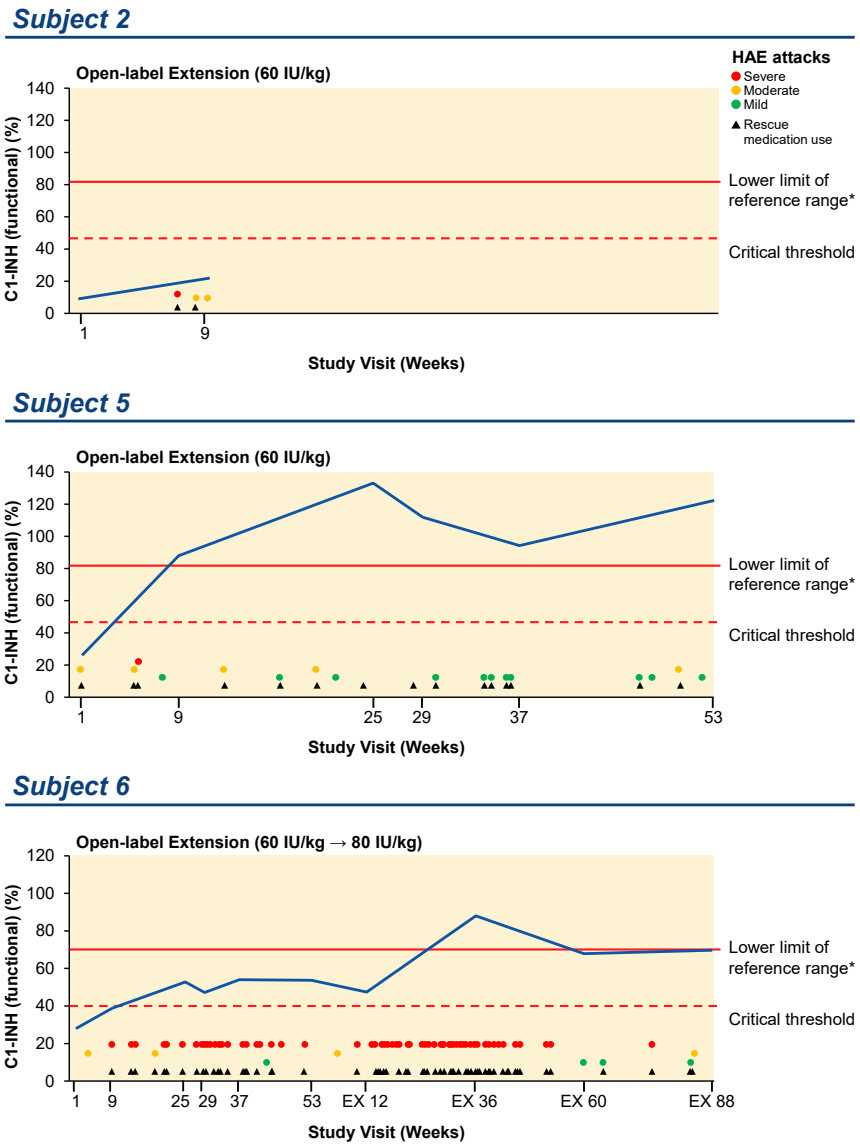


**Figure 2.** HAE attack patterns and C1-INH functional activity in nonresponding patients 65 years old and above. Reference range: 70% to 130%. C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema.

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## Supplementary Data

**eTable 1**
Adverse Events Among Patients 65 Years Old and Above Treated With Subcutaneous C1 Esterase Inhibitor

| Patient | Concomitant Chronic medications | Adverse events during prophylaxis |
|---|---|---|
| 1 | Levothyroxine, SSRI, ondansetron, insulin, antipropulsive, gabapentin, iron, magnesium, PPI, hydroxychloroquine | Dehydration[a], hypokalemia[a], *injection site pain*, abdominal discomfort, hypotension, soft-tissue injury, aortic arteriosclerosis, UTI (2), bronchitis, lumbar spinal stenosis, blood potassium decreased, blood urea increased, vitamin B12 deficiency |
| 2 | Albuterol, atenolol, duloxetine, fluticasone propionate/ salmeterol, tiotropium bromide, lorazepam, simvastatin, trazodone | *Injection site pain*, oropharyngeal pain, *injection site hemorrhage, injection site induration* |
| 3 | Cetirizine, fluticasone propionate | Hypothyroidism, *injection site bruising,* URTI, vertigo |
| 4 | Verapamil, atorvastatin, liraglutide, glipizide, zolpidem tartrate, trazodone, amphetamine | *Injection site bruising* (2) |
| 5 | PPI, ranitidine, ipratropium bromide | *Injection site hematoma*, UTI, nasopharyngitis, sinusitis, laryngitis |
| 6 | Metformin, glimepiride, insulin, carvedilol, valsartan, atorvastatin, canagliflozin | Pneumonia[a], HAE attack leading to hospitalization[a], depression, diarrhea |
| 7 | Metoprolol, HCTZ | None reported |
| 8 | Zolpidem tartrate, metoprolol, rosuvastatin, ezetimibe, cetirizine | Hypertonia, pharyngitis, toothache, periostitis, herpes zoster, conjunctivitis |
| 9 | Metoprolol, aspirin, insulin, HCTZ, sulfonamides, allopurinol, metformin, liraglutide, potassium | Postprocedural swelling, diarrhea, pain in extremity, thermal burn, arthralgia, osteoarthritis |
| 10 | Losartan, glipizide, HCTZ, metformin, amlodipine, SSRI, pravastatin | Musculoskeletal pain, ligament sprain |

Abbreviations: C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; HCTZ, hydrochlorothiazide; PPI, proton-pump inhibitor; SSRI, selective serotonin reuptake inhibitor; URTI, upper respiratory tract infection; UTI, urinary tract infection.
NOTE. Italicized text indicates treatment-related AEs.
[a]Unrelated serious adverse event.

**eTable 2**
C1 Esterase Inhibitor Functional Levels (%) During Prophylactic Treatment With Subcutaneous C1 Esterase Inhibitor in Patients 65 Years Old and Above

| Patient | Open-label extension | | | | | | United States extension | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 (day 1) | Week 9 | Week 25 | Week 29 | Week 37 | Week 53 | Week 12 | Week 36 | Week 60 | Week 88 |
| 1 | 68.6 | 56.8 | 41.2 | 41.4 | 52.8 | - | - | - | - | - |
| 2 | 8.9 | 21.4 | - | - | - | - | - | - | - | - |
| 3 | 10.0 | 46.2 | 45.8 | 40.6 | 68.7 | 56.7 | 65.2 | 60.8 | 56.7 | 57.3 |
| 4 | 23.6 | 36.1 | 24.2 | 28.1 | 48.9 | 30.6 | 32.4 | 38.0 | - | - |
| 5 | 25.7 | 88.2 | 133.3 | 112.3 | 94.3 | 122.3 | - | - | - | - |
| 6 | 29 | 38.7 | 53.1 | 47.2 | 53.8 | 53.9 | 48.0 | 88.5 | 68.4 | 69.9 |
| 7 | 15.5 | 73.1 | 83.7 | 80.7 | 87.1 | 77.4 | 69.3 | 73.0 | 65.3 | 72.0 |
| 8 | 24.5 | 66.6 | 79.2 | 64.5 | 69 | 60.3 | - | - | - | - |
| 9 | 25.7 | 28.3 | 26.8 | 38 | 26.5 | 21.9 | - | - | - | - |
| 10 | 19.6 | 45.8 | 46.1 | 69.3 | 71 | 77 | 37.6 | 46.0 | 62.8 | 48.0 |
| Mean | 25.1 | 50.1 | 59.3 | 58.0 | 63.6 | 62.5 | 50.5 | 61.26 | 63.3 | 61.8 |