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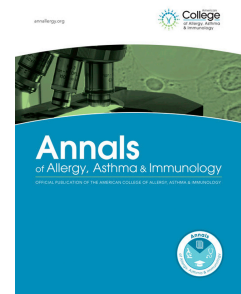
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CLINICAL RESEARCH STUDY**Long-term Safety and Efficacy of Subcutaneous C1-Inhibitor in Older Patients With Hereditary Angioedema**

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Author Contributions

JB, MR, LS, HF, AB, HF, JA, and EA-P helped develop the first and subsequent drafts. IJ, IP, and HF provided and reviewed key data analyses. WY and JB reviewed all drafts. All authors approved the final version.

Declaration of Interest

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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BACKGROUND Patients ≥ 65 years old with hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency may have an altered response to treatment and be at higher risk for treatment-related adverse events (AEs) due to comorbidities and polypharmacy.

OBJECTIVE Investigate the safety and efficacy of subcutaneous (SC) C1-INH in patients ≥ 65 years old treated in an open-label extension of a phase 3 trial.

METHODS Eligible patients (≥ 4 attacks over 2 consecutive months) were randomized to receive twice-weekly C1-INH (SC) 40 IU/kg or 60 IU/kg for 52 to 140 weeks. Safety endpoints and efficacy outcomes were evaluated for patients aged ≥ 65 and < 65 years.

RESULTS Of 126 subjects treated, 10 were ≥ 65 years old (mean age [range], 68 [65-72 years]). Eight of 10 subjects had multiple comorbidities; 6/10 were taking > 5 non-HAE-related drugs concomitantly. AEs occurring in > 1 subject 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 subjects ≥ 65 years old experienced unrelated serious AEs (dehydration and hypokalemia in one and pneumonia and an HAE attack leading to hospitalization in another). Six of 9 evaluable subjects were responders, with $\geq 50\%$ reduction in HAE attacks versus pre-study; 6/10 had < 1 attack/4 weeks and 3 were attack-free (median attack rate, 0.52 attacks/month).

CONCLUSION C1-INH (SC) was well tolerated and effective in the management of HAE in these subjects ≥ 65 years old with multiple comorbid conditions and polypharmacy.

1 INTRODUCTION

2 Hereditary angioedema (HAE) due to C1-esterase inhibitor (C1-INH) deficiency (C1-INH-HAE)
3 is a rare autosomal-dominant disorder characterized by recurrent, debilitating attacks of
4 nonpruritic bradykinin-mediated angioedema that commonly affect the tissues of the face, trunk,
5 extremities, and genitalia, as well as the upper airways and gastrointestinal tract.¹⁻³ The exact
6 prevalence of C1-INH-HAE is unknown, but has been estimated to be 1.5 per 100,000.⁴
7 Symptoms usually commence in childhood, worsen around puberty, and persist throughout the
8 patient's life.^{3,5} HAE is associated with significant morbidity and can be fatal if laryngeal
9 angioedema is not managed promptly and appropriately as it can lead to asphyxiation.^{6,7} HAE
10 attacks are unpredictable, making it difficult for patients to plan for travel or other life events,
11 and often cause anxiety about future attacks.^{8,9} In patients who are untreated, frequency of
12 attacks can range from a few attacks per year to 1 or more attacks per week.^{1-3,10} Emotional
13 stress, physical exertion, trauma, hormonal changes, and infection have been reported to trigger
14 HAE attacks, but they can occur without any identifiable stimulus.^{11,12}
15 The treatment of HAE in older adults (patients ≥ 65 years old) presents several challenges. Age-
16 related changes in physiology and in pharmacokinetics (absorption, distribution, metabolism, and
17 excretion) may affect the safety profile of a drug in older patients, putting them at higher risk for
18 treatment-related adverse events (AEs).^{13,14} Patients ≥ 65 years old are more likely to have
19 multiple comorbidities, leading to polypharmacy, which in turn may increase the likelihood of
20 drug-related disease and drug-drug interactions.¹⁴ The presence of comorbidities may also affect
21 the clinical course of HAE, especially in female patients. In a retrospective study of 150 patients
22 (mean age, 44.1 years; 16 patients ≥ 65 years old), Martinez-Saguer et al reported that the annual
23 mean attack frequency was greater in patients with concomitant diseases, particularly in female

patients (48.3 attacks/year in female patients with concomitant disease vs 28.6 attacks/year in female patients without concomitant disease).¹⁵ In the same study, the prevalence of comorbidities was higher in patients ≥ 65 years old, as expected.

The 2017 World Allergy Organization (WAO) guidelines for the management of HAE do not provide specific recommendations for older patients with HAE, but plasma-derived (pd) C1-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 (SC) formulation of C1-INH (C1-INH [SC] 60 IU/kg, Haegarda[®], CSL Behring, Marburg, Germany) was approved by the US Food and Drug Administration (FDA) for routine prophylaxis to prevent HAE attacks in adolescents and adults.¹⁸ The efficacy and safety of C1-INH (SC) have been demonstrated in the pivotal, placebo-controlled phase 3 COMPACT trial (Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy), as well as 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 C1-INH (SC) 60 IU/kg twice weekly resulted in a 95% median reduction in HAE attacks relative to placebo and a >99% median reduction in rescue medication use.¹⁹ In the OLE of this trial, the median annualized attack rates were 1.3 and 1.0, and annual median rescue medication use was 0.2 and 0.0 times per year, respectively, with the C1-INH (SC) 40 IU/kg and 60 IU/kg doses.²⁰ In addition, long-term prophylactic therapy with C1-INH (SC) was well tolerated, with a low incidence of AEs (11.3 and 8.5 events per patient-year with C1-INH [SC] 40 IU/kg and 60 IU/kg, respectively).²⁰

In the current post-hoc analysis, we evaluated the efficacy and safety of C1-INH (SC) in the subgroup of subjects with C1-INH-HAE ≥ 65 years old treated in the OLE of the COMPACT trial to determine whether older age and comorbidities might affect the efficacy and safety profile of C1-INH (SC).

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, as well as C1-INH (SC)-naïve patients. Eligible patients (age ≥ 6 years with ≥ 4 attacks over 2 consecutive months before enrollment in the OLE or the COMPACT trial) were randomly assigned to receive C1-INH (SC) 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 (**Figure 1**). The study included 2 treatment periods (TPs)—during the first treatment period (TP1, 24 weeks), patients experiencing ≥ 12 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 TP2 (28 weeks), patients experiencing ≥ 3 attacks within an 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 C1-INH (SC).²⁰ The primary, prespecified endpoints were person-time incidence rates of related serious AEs; AEs leading to premature discontinuation; AEs of special interest (thromboembolic events, anaphylaxis); HAE attacks resulting in hospitalization; injection-site reactions graded severe by the investigator; and the development of anti-C1-INH antibodies.²⁰ Efficacy endpoints included

the percentage of patients with <1 attack per 4-week period, and the percentage of responders (patients with $\geq 50\%$ reduction in attacks relative to the pre-study period).²⁰

In this post-hoc analysis, patients were analyzed by age subgroups (<65 years and ≥ 65 years at OLE study entry), based on the FDA definition of a geriatric population. Safety outcomes and the following efficacy endpoints were evaluated for these 2 age subgroups: time-normalized number of HAE attacks, percentage of responders, and percentage of patients with <1 attack per 4-week period. Informed consent and IRB review was not required for this study as existing data was utilized for post-hoc analysis.

RESULTS

Baseline Demographic and Disease Characteristics

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

All 10 subjects ≥ 65 years old had ≥ 1 comorbidity, with the majority (8/10) having multiple comorbidities: 8 had hypertension, 5 had diabetes mellitus, and 6 had hyperlipidemia/hypercholesterolemia. In addition, 4 subjects had anxiety and/or depression

disorders. Based on World Health Organization definitions of overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) and obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$),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 subjects taking more than 5 drugs for these comorbidities during the study (**Table 2**).

In subjects ≥ 65 years old treated with C1-INH (SC), the median (range) duration of treatment in the efficacy evaluation period was 75 weeks (~ 6 –133 weeks). Two of the C1-INH (SC)-treated subjects were randomized to the 40 IU/kg dose and 8 to the 60 IU/kg dose. Subjects 3 and 6 had their dose up-titrated from 40 IU/kg and 60 IU/kg, respectively. Seven subjects were previously enrolled in the placebo-controlled COMPACT trial and 3 were naive to C1-INH (SC) treatment.

No subjects in the older subgroup discontinued due to an AE. One 68-year-old subject withdrew from the study after ~ 8 weeks because the “study was too much of a hassle.” Another subject discontinued after ~ 2 years due to personal issues and a third withdrew after ~ 1 year (no reason provided).

Safety Outcomes

In the overall study population, as well as in the subgroup of subjects ≥ 65 years old, C1-INH (SC) was well tolerated. Local injection-site reactions were the most common AEs and occurred in 5 subjects. Specific AEs occurring in >1 subject in the subgroup aged ≥ 65 years old included injection-site bruising ($n = 2$, related), injection-site pain ($n = 2$, related), urinary tract

infection (n = 2, unrelated), and diarrhea (n = 2, unrelated) (**Table 3 and Supplementary Table 1**).

In the overall population (N = 126), 12 serious AEs (all unrelated to treatment) occurred in 9 subjects, 2 of whom were ≥ 65 years old. Subject 1, a 67-year-old female, experienced dehydration and hypokalemia during treatment with C1-INH (SC) 40 IU/kg. The events resolved and did not lead to treatment discontinuation. Subject 6, a 68-year-old male, experienced pneumonia during treatment with C1-INH (SC) 60 IU/kg 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 subjects in either age subgroup.

Efficacy Outcomes

Of the 9 subjects in the older subgroup evaluable for the responder analysis, 6 were classified as responders, with $\geq 50\%$ reduction in the time-normalized number of HAE attacks during treatment with C1-INH (SC) relative to the pre-study period (**Table 4**). Two subjects did not experience a decrease in attacks and 1 subject experienced a 42% reduction. Six of 10 subjects experienced < 1 attack per 4-week period and 3 were attack free. The mean number of HAE attacks/month decreased from 2.71 before the study to 0.86 with C1-INH (SC). For comparison, among subjects < 65 years old (n = 116), 106 (94%) of the 113 evaluable for the analysis were classified as responders, and 98 (85%) had < 1 attack/week; 47 (40%) were attack-free. The mean number of HAE attacks/month decreased from 4.40 before the study to 0.42 with C1-INH (SC).

The 3 nonresponding subjects had multiple comorbidities, including hypertension, and were taking multiple concomitant medications. One nonresponder subject (Subject 2) withdrew from

the OLE after ~8 weeks (patient choice), experiencing 3 HAE attacks over the study evaluation period (**Figure 2**, first panel). The second nonresponder (Subject 5) completed the OLE study and reported mostly mild and moderate attacks, with only 1 severe attack during the 1 year in the study; of note, this subject's trough steady-state functional C1-INH level was above the normal range through most of the year of treatment (**Figure 2**, second panel). The third nonresponder, Subject 6, reported mild to severe attacks, even when functional C1-INH levels were >40% of normal (**Figure 2**, third panel); the frequency of attacks decreased when functional C1-INH levels increased to the lower limit of normal.

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

DISCUSSION

In this post-hoc analysis of subjects ≥ 65 years old with C1-INH-HAE treated prophylactically with C1-INH (SC) in the OLE of the COMPACT trial, all subjects had multiple comorbidities and polypharmacy, yet C1-INH (SC) was found to be generally safe and well tolerated. No subject in this subgroup discontinued due to an AE. In addition, C1-INH (SC) was effective, with 3 of 10 subjects ≥ 65 years old having no attacks for ~1 to 2.6 years and 6 of 10 having an average of <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 treatment due to concurrent comorbidities and their associated medications.¹³⁻¹⁵ In subjects ≥ 65 years old treated in the present 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 <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 subjects in the older subgroup had multiple comorbidities.

In the 2017 WAO 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 (IV) pdC1-INH therapy used as 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 the present post-hoc analysis are consistent with the Berinert[®] registry study²⁵ and indicate that the SC formulation of C1-INH is also well tolerated and safe as prophylactic treatment in adolescents and adults, including patients ≥ 65 years old. The most common treatment-related AEs were 1 to 3 mild injection-site reactions per subject, which occurred in 5 of 10 subjects, 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 subjects ≥ 65 years old, despite the inherent 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 subjects ≥ 65 years old.

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

All subjects 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.^{27,28} For such patients, C1-INH (SC) is a convenient alternative to C1-INH (IV) therapy and obviates the need for venous access.

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

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276

Tables

Table 1. Baseline Demographic Characteristics by Age Group

Characteristic	Subjects <65 Years Old (n = 116)	Subjects ≥65 Years Old (n = 10)
Age, years		
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 C1-INH (SC) treatment, mean (SD)	4.4 (3.1)	2.7 (2.5)

BMI = body mass index; C1-INH = C1-inhibitor; SC = subcutaneous; SD = standard deviation.

Table 2. Demographic and Disease Characteristics of Study Subjects ≥ 65 Years Old

Subject	Gender	Age	BMI, kg/m ²	Chronic Comorbidities	Concomitant Chronic 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 disc 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 disc 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

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.

Table 3. AE Profile of C1-INH (SC) in Subjects ≥ 65 Years Old

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

AE = adverse event; C1-INH = C1-inhibitor; SC = subcutaneous.

Table 4. Efficacy Outcomes in Subjects ≥ 65 Years Old Treated Long-term With C1-INH (SC)

Subject	C1-INH (SC) Treatment Status	C1-INH (SC) Dose at Randomization (IU/kg)	Evaluation Period (weeks) During C1-INH (SC) Exposure*	Responder ($\geq 50\%$ reduction in attacks vs pre-study)	<1 Attack/ 4-Week Period
1	Previously treated	40	48.7	Yes	No
2	Previously treated	60	6.1†	No	No
3	Previously treated	40‡	117.4	Yes	Yes
4	Previously treated	60	99.1	Yes	Yes
5	Previously treated	60	50.4	No	No
6	Previously treated	60‡	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§ (attack free)	Yes (attack free)

C1-INH = C1-inhibitor; NE = not evaluable; SC = subcutaneous. *The treatment evaluation period began at week 3 of treatment. †Subject withdrew early from the study due to personal reasons. ‡Subject was up-titrated. §Due to an investigator data entry error, the attack rate during C1-INH (IV) prophylaxis (0 attacks) was recorded as the pre-study attack rate; therefore, a percent reduction in attacks could not be calculated for this patient.

Figure 1. COMPACT OLE study design. C1-INH (SC) = subcutaneous C1-inhibitor

Figure 2. HAE attack patterns and C1-INH functional activity in nonresponding subjects ≥ 65 years old. *Reference range: 70%–130%. C1-INH = C1-inhibitor; HAE = hereditary angioedema

Figure 1. COMPACT OLE study design. C1-INH (SC) = subcutaneous C1-inhibitor

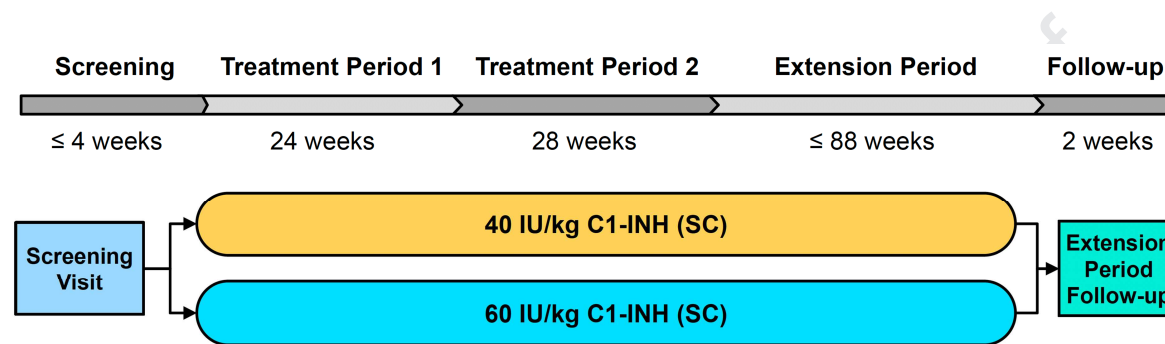
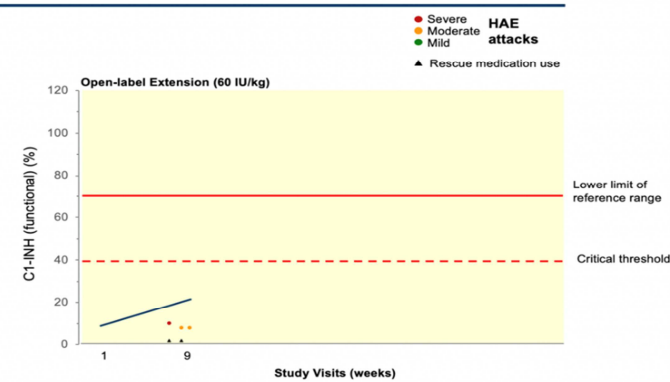
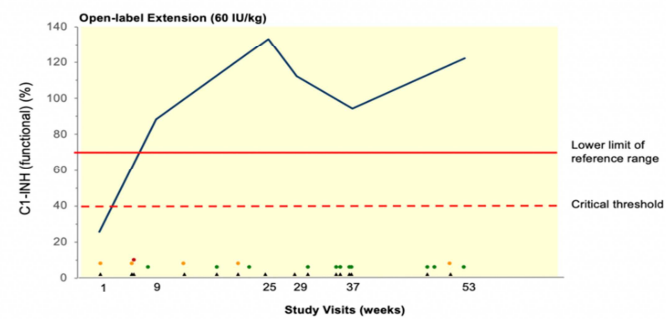


Figure 2. HAE attack patterns and C1-INH functional activity in nonresponding subjects ≥ 65 years old. *Reference range: 70%–130%. C1=INH = C1=inhibitor; HAE = hereditary angioedema

Subject 2**Subject 5****Subject 6**