

Subcutaneous C1-esterase inhibitor to prevent hereditary angioedema attacks: Safety findings from the COMPACT trial

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ABSTRACT

Background: The first subcutaneous (SC) C1-esterase inhibitor concentrate (C1-INH) was approved by the U.S. Food and Drug Administration in June 2017 as routine prophylaxis to prevent hereditary angioedema attacks in adolescents and adults at a dose of 60 IU/kg twice weekly based on the phase III Clinical Study for Optimal Management of Preventing Angioedema With Low-volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT) trial.

Objective: This article aimed to evaluate the relationship of the C1-INH (SC) dose regimens tested in the COMPACT trial (40 IU/kg and 60 IU/kg twice weekly) and the occurrence of adverse events (AEs).

Methods: Patients were instructed to record any AEs in their e-diary daily. Safety and tolerability were assessed based on reported AEs, including injection-site reactions (ISRs); unsolicited AEs (AEs other than ISRs); serious AEs; thrombotic, thromboembolic, anaphylactic, hypersensitivity, sepsis, and bacteremia events; inhibitory antibodies to C1-INH; and clinically significant abnormalities in laboratory assessments. Information on ISRs was specifically solicited.

Results: No relationship between the dose of C1-INH (SC) and the incidence of ISRs or unsolicited AEs was observed. The proportion of injections followed by at least one ISR was 12% with C1-INH (SC) 40 IU/kg versus 5% with 60 IU/kg and 6% with placebo. No ISRs were serious or led to treatment discontinuation, and all resolved. There were no anaphylaxis, thromboembolic, sepsis, or bacteremia events reported during treatment with C1-INH (SC). All hypersensitivity AEs were nonserious, and the majority were assessed as being unrelated to treatment. No inhibitory antibodies to C1-INH were observed.

Conclusion: C1-INH (SC) is safe and well tolerated with no dose-dependent safety concerns, as demonstrated in the COMPACT trial.

Clinical trial NCT01912456, www.clinicaltrials.gov

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Hereditary angioedema (HAE) is an autosomal dominant genetic disorder that results from mutations in the *SERPINC1* gene, which lead to a functional deficiency in C1-esterase inhibitor (C1-INH). HAE is characterized by recurrent, disabling attacks of nonpruritic edema that affect subcutaneous tissues of the face, trunk, genitalia, and extremities, and/or sub-

mucosal tissues of the respiratory and gastrointestinal tracts.^{1,2} Attacks can be painful, disfiguring, and sometimes fatal. Given the highly variable presentation and course of HAE, international guidelines for its management recommend an individualized treatment approach, with the goal of reducing the number and severity of attacks and restoring the patient's quality of life.^{3–5} These guidelines also indicate that the decision to initiate long-term prophylactic treatment be individualized based on several patient and disease factors.^{3–5} In the most recent international guidelines, C1-INH replacement therapy is indicated as a first-line treatment for patients with HAE who require long-term prophylaxis.³

In Europe, plasma-derived C1-INH has been used for HAE treatment for >30 years, and its efficacy and safety are well established.^{6–10} In the United States, an intravenously (IV) administered plasma-derived C1-INH formulation has been available since 2008 for the prevention of HAE attacks, having demonstrated a reduction in attack frequency and severity relative to placebo.¹¹ In June 2017, the U.S. Food and Drug Administration approved the first subcutaneously (SC) administered human plasma-derived C1-INH concen-

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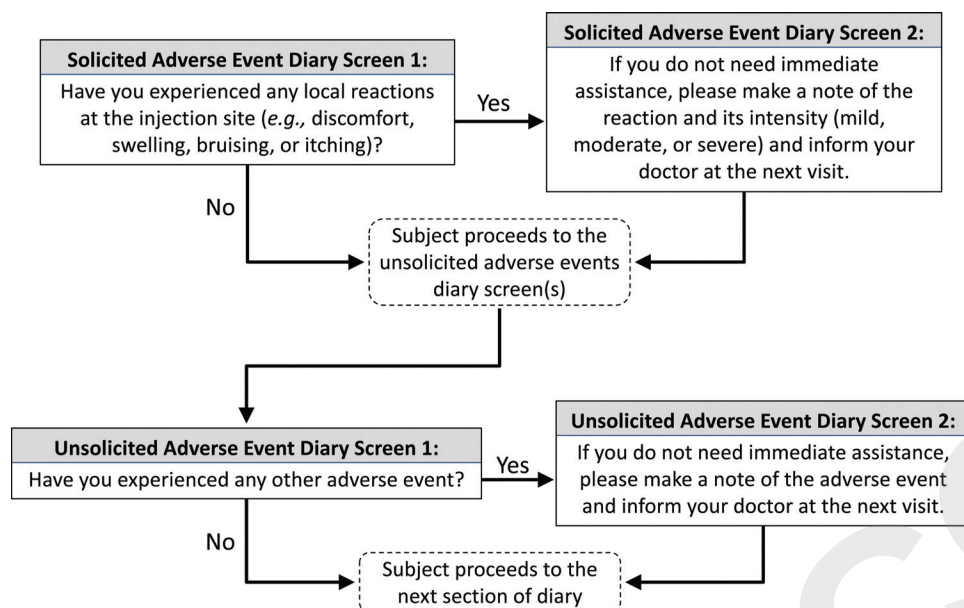


Figure 1. Hereditary angioedema e-diary screens for recording adverse events.

trate (C1-INH [SC], HAEGARDA; CSL Behring, Marburg, Germany) at a dose of 60 IU/kg for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.¹²

Approval was based primarily on results from the Clinical Study for Optimal Management of Preventing Angioedema With Low-volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT) trial, a phase III, randomized, multicenter, double-blind, placebo-controlled, crossover study.^{12,13} Patients (ages ≥ 12 years) who experienced four or more HAE attacks over 2 consecutive months within 3 months before screening were eligible for the COMPACT trial. Patients self-administered twice-weekly injections of C1-INH (SC) 40 IU/kg or 60 IU/kg for 16 weeks and high-volume or low-volume placebo for 16 weeks in a crossover manner. The 40 IU/kg and 60 IU/kg doses were equivalent to 3000 IU and 4500 IU, respectively, for a patient with a bodyweight of 75 kg.¹³ The study was approved by the institutional review board or ethics committee at each participating center, and was performed in accordance with good clinical practice, the Declaration of Helsinki, and local regulatory requirements. Written informed consent was obtained from all patients or their legal guardians.

The 40- and 60-IU/kg twice-weekly dosing regimens were expected to achieve a mean steady-state trough C1-INH functional activity of $\geq 40\%$, a threshold proposed to be associated with the prevention of HAE attacks.^{14,15} Indeed, the mean steady-state C1-INH functional activity (from weeks 3 to 14) ranged from 45 to 49% with C1-INH (SC) 40 IU/kg and from 63 to 69% with C1-INH (SC) 60 IU/kg. There was a dose-dependent increase of ~ 35 to 46% in mean steady-state C1-INH functional activity with C1-INH (SC) 60 IU/kg

compared with 40 IU/kg. At 60 IU/kg, C1-INH functional activity and C1-INH levels approached the lower limit of normal (70%).¹³

In a recently published exposure-response analysis, an inverse relationship between plasma C1-INH functional activity and risk of an HAE attack was established.¹⁶ As reported previously,¹³ treatment with C1-INH (SC) resulted in a significant reduction in the time-normalized number of HAE attacks versus placebo, with the 60-IU/kg dose resulting in greater reductions than the 40-IU/kg dose. Treatment with C1-INH (SC) 60 IU/kg also resulted in greater reductions in the monthly use of rescue medication compared with the 40-IU/kg dose.¹³ The objective of the current analysis of the COMPACT trial data was to evaluate the relationship of C1-INH (SC) dosing to the incidence of adverse events (AE).

METHODS

During the COMPACT trial, patients were instructed to record daily any AEs in their e-diary (Fig. 1). Safety and tolerability were assessed based on AEs, including injection-site reactions (ISRs); unsolicited AEs (AEs other than ISRs); serious AEs; thrombotic, thromboembolic, anaphylactic, hypersensitivity, sepsis, and bacteremia events; inhibitory antibodies to C1-INH; and clinically significant abnormalities in laboratory assessments.

A plasma-derived C1-INH formulation (Berinert; CSL Behring, Marburg, Germany) that is administered IV has been in clinical use for >30 years. The key feature that differentiates C1-INH (SC) from this formulation is its SC route of administration. The safety assessments in the COMPACT trial, therefore, focused

Table 1 Summary of ISRs reported with placebo and C1-INH (SC)

	Combined Placebo (86 patients, 2454 injections)*		40 IU/kg C1-INH (SC) (43 patients, 1307 injections)		60 IU/kg C1-INH (SC) (43 patients, 1320 injections)	
	Patients, no. (%)	ISRs, no.	Patients, no. (%)	ISRs, no.	Patients, no. (%)	ISRs, no.
Any ISR	21 (24)	212	12 (28)	274	15 (35)	103
Severity						
Mild	20 (23)	201	11 (26)	270	15 (35)	88
Moderate	5 (6)	10	2 (5)	4	5 (12)	15
Severe	1 (1)	1	0	0	0	0
Duration						
≤1 day	16 (19)	191	12 (28)	247	13 (30)	64
>1 day to ≤2 days	4 (5)	10	5 (12)	14	3 (7)	29
>2 days to ≤3 days	0	0	1 (2)	1	1 (2)	3
>3 days	8 (9)	11	6 (14)	12	5 (12)	7
Outcome						
Resolved	21 (24)	212	12 (28)	274	15 (35)	103
Not resolved	0	0	0	0	0	0
Seriousness						
Nonserious	21 (24)	212	12 (28)	274	15 (35)	103
Serious	0	0	0	0	0	0
Leading to discontinuation	0	0	0	0	0	0

ISR = Injection-site reaction; C1-INH = C1-esterase inhibitor; SC = subcutaneous.

*Combined low- and high-volume placebo.

on ISRs because these were potentially a source of AEs expected with this SC formulation, and information about ISRs was specifically solicited. The patients were asked to record ISRs in their e-diary by answering the following question (yes or no): "Have you experienced any local reactions at the injection site (e.g., discomfort, swelling, bruising, or itching)?" Patients were instructed to take notes (outside of the e-diary) to describe any ISRs they experienced and communicate that information to their investigator. Investigators reviewed the e-diary with the patient and then documented AEs, including time of onset and resolution, severity (mild, moderate, or severe), relationship to treatment, action taken, and outcome. For ISRs, each symptom was entered as an independent AE (*i.e.*, multiple ISRs could be reported for a single injection of C1-INH [SC] or placebo).

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Missing severity or outcome designations were classified as unknown. AEs with a missing causality assessment were considered related to treatment.

RESULTS

Safety Population and Exposure

A total of 86 patients received one or more doses of C1-INH (SC): 43 patients received 40 IU/kg and 43

received 60 IU/kg twice weekly. The mean duration of exposure to C1-INH (SC) was similar with 40 IU/kg and with 60 IU/kg (16.3 weeks and 16.0 weeks, respectively). A total of 1307 injections of C1-INH (SC) at 40 IU/kg and 1320 injections at 60 IU/kg were administered.

Solicited AEs: ISRs

ISRs were the most common category of AEs documented in the COMPACT trial (Table 1). ISRs were reported in similar percentages of patients across all treatments, and there was no clear relationship between the dose of C1-INH (SC) and incidence of ISRs: 274 ISRs were reported in 28% of patients (12/43) treated with C1-INH (SC) 40 IU/kg; 103 ISRs were reported in 35% of patients (15/43) treated with C1-INH (SC) 60 IU/kg; and 212 ISRs were reported in 24% of patients (21/86) during the combined placebo periods. ISRs reported in >5% of patients during treatment with C1-INH (SC) were injection-site erythema, pain, edema, induration, bruising, and swelling (Table 2).

In the study, 12% of 1307 injections with C1-INH (SC) 40 IU/kg and 5% of 1320 injections with C1-INH (SC) 60 IU/kg were followed by at least one ISR compared with 6% of 2454 placebo injections. Important to the interpretation of these findings was that a small

Table 2 ISRs in $\geq 5\%$ of the patients

ISR Term	Combined Placebo*		40 IU/kg C1-INH (SC)		60 IU/kg C1-INH (SC)	
	(86 patients, 2454 injections)		(43 patients, 1307 injections)		(43 patients, 1320 injections)	
	Patients, no. (%)	ISRs, no.	Patients, no. (%)	ISRs, no.	Patients, no. (%)	ISRs, no.
Erythema	12 (14)	60	7 (16)	86	9 (21)	20
Pain	9 (11)	43	7 (16)	90	7 (16)	19
Edema	3 (4)	63	5 (12)	60	0 (0)	0
Swelling	4 (5)	24	1 (2)	1	4 (9)	39
Induration	2 (2)	4	3 (7)	8	4 (9)	6
Bruising	5 (6)	7	2 (5)	5	4 (9)	5

ISR = Injection-site reaction; C1-INH = C1-esterase inhibitor; SC = subcutaneous.

*Combined low- and high-volume placebo.

number of patients contributed a disproportionately large number of ISRs to the total event counts, partly a result of the methodology used to document and assess ISRs. Three patients contributed 70% of all ISRs (193/274) reported with C1-INH (SC) 40 IU/kg and 83% of all ISRs (123/149) reported with high-volume placebo. Similarly, a single patient contributed 27% of all ISRs (28/103) reported with C1-INH (SC) 60 IU/kg and 65% of all ISRs (41/63) reported with low-volume placebo.

Of the ISRs reported during treatment with C1-INH (SC) 40 IU/kg or 60 IU/kg, none were of severe intensity, were assessed as serious, or led to treatment discontinuation; all ISRs were reported to be resolved (Table 1). The majority of ISRs with C1-INH (SC) were mild and resolved within 24 hours of onset.

Unsolicited AEs

As with ISRs, there was no clear relationship between the incidence of unsolicited AEs (AEs other than ISRs) and the C1-INH (SC) dose. Of the unsolicited AEs reported with C1-INH (SC), 68 occurred in 23 patients treated with C1-INH (SC) 40 IU/kg and 54 occurred in 25 patients treated with C1-INH (SC) 60 IU/kg. During the placebo periods, 132 unsolicited AEs were reported in 48 patients. The majority of unsolicited AEs were mild and unrelated to treatment. During treatment with 40 IU/kg, 97.1% of unsolicited AEs were mild or moderate and 86.8% were assessed as unrelated to C1-INH (SC). During treatment with C1-INH (SC) 60 IU/kg, 94.4% of unsolicited AEs were mild or moderate and 85.2% were assessed as unrelated to C1-INH (SC). Similarly, with placebo (low and high volume), 93.9% of unsolicited AEs were mild or moderate and 97.0% were assessed as unrelated to treatment. Nasopharyngitis was the most commonly reported unsolicited AE. All nasopharyngitis events were considered unrelated to treatment and were mild or moderate.

No serious AEs occurred with C1-INH (SC) 60 IU/kg; a single serious AE (urosepsis) assessed as unrelated to treatment occurred with C1-INH (SC) 40 IU/kg. During the placebo periods, three serious unsolicited AEs occurred in two patients.

Anaphylaxis and Hypersensitivity

No case of anaphylaxis occurred with either dose of C1-INH (SC) or high- or low-volume placebo. Potential hypersensitivity events were identified, regardless of relatedness, by comparing all AEs documented in the study against a list of prospectively identified hypersensitivity AE terms (*i.e.*, a Standardized MedDRA version 18.0. query). AEs identified using the query occurred in eight patients during C1-INH (SC) treatment and seven patients during placebo treatment. All hypersensitivity AEs were nonserious, and the majority were assessed as unrelated to treatment (all relatedness assessments were performed by blinded investigators).

Hypersensitivity AEs occurred in three patients on C1-INH (SC) 60 IU/kg (urticaria, rash, and cough) and in five patients on C1-INH (SC) 40 IU/kg (urticaria, rash, pruritus, caffeine allergy, conjunctivitis, and injection-site urticaria [classified as an ISR]). Hypersensitivity AEs during the combined placebo periods included rash, blister, dyspnea, asthma, sneezing, seasonal allergy, conjunctivitis, and eosinophilia. The rash events included one unrelated event with a reported term of "facial rash" with C1-INH (SC) 40 IU/kg and one unrelated event with a reported term of "skin rash on back from tattoo procedure" during C1-INH (SC) 60 IU/kg treatment.

Nonserious events of urticaria were reported in two patients: three unrelated events in a patient on C1-INH (SC) 40 IU/kg and six events in a patient on C1-INH (SC) 60 IU/kg, which were assessed as related to treatment. Before the study, the patient who experienced

six urticaria events received C1-INH (IV) (Berinert; CSL Behring) for acute treatment of HAE attacks. The patient received the first four doses of C1-INH (SC) without reported AEs. With the fifth administration of C1-INH (SC), the first event of urticaria was reported, and the subsequent three administrations were followed by events at additional locations (arms, legs, abdomen). These were isolated symptoms. Notably, the urticaria developed the day after each C1-INH (SC) injection and lasted ~1 to <3 days. The patient discontinued C1-INH (SC) and did not proceed to the second treatment period (placebo phase). The patient subsequently experienced two additional events of urticaria 6 days and 11 days after the last dose. The patient was then restarted on C1-INH (IV) to treat HAE attacks, with no further occurrence of urticaria reported.

Thromboembolic Events

No thromboembolic event occurred with C1-INH (SC) at either dose. One patient experienced a pulmonary embolism during treatment with placebo and before any C1-INH (SC) was administered.

Sepsis and/or Bacteremia

No sepsis or bacteremia event related to C1-INH (SC) or to placebo was reported. One patient, as previously mentioned, experienced urosepsis with C1-INH (SC) 40 IU/kg; however, the event was assessed as unrelated to treatment due to alternative etiology (bacterial infection on a background of chronic urinary tract infections, diabetes mellitus, and lupus). The patient subsequently completed the study.

Immunogenicity

No inhibitory antibodies to C1-INH were observed in any patient before administration of C1-INH (SC) during the study, during treatment with C1-INH (SC) or placebo, or in follow-up measurements. No association was identified between treatment with C1-INH (SC) and detection of noninhibitory (non-neutralizing) antibodies to C1-INH.

DISCUSSION

Overall, injections of C1-INH (SC) were safe and well tolerated. Results of the present analysis indicated that there were no dose-dependent safety concerns with C1-INH (SC) in the COMPACT trial.

ISRs were the most commonly reported AEs with both doses of C1-INH (SC) and with placebo. This finding was partly due to the methodology used, whereby ISRs were specifically solicited and a single injection could be associated with multiple AEs. The 60 IU/kg dose of C1-INH (SC) was not associated with a higher rate of ISRs or with any different type of ISR compared with the 40-IU/kg dose. The proportion of

injections followed by ISRs was comparable between active treatment and placebo. No clear relationship between the dose of C1-INH (SC) and the incidence of ISRs or unsolicited AEs was observed.

The incidence of hypersensitivity reactions reported with SC administered biologics varies widely. Drug-related risk factors for hypersensitivity reactions include the degree of humanization, glycosylation pattern, type of cells from which the biologic is derived, and excipients with potential to induce allergic reactions.¹⁷ Because the C1-INH preparation discussed here is a human plasma-derived protein that has a well-established safety profile when administered *via* IV, a significantly increased incidence of hypersensitivity reactions during SC administration was unlikely, which was clearly reflected by the findings of the COMPACT trial. Furthermore, no anaphylactic reactions were reported with C1-INH (SC), no dose-dependent safety concern emerged with respect to hypersensitivity reactions, and no inhibitory antibodies were detected in any patient treated with C1-INH (SC) during the study. The low antigenic potential of plasma-derived C1-INH products such as C1-INH (SC) may be due to the production of some C1-INH protein still seen in patients with HAE; therefore, the exogenous protein is not entirely unfamiliar to the immune system.¹⁸

Allergic hypersensitivity is restricted to reactions secondary to an immunologic process, whereas the diagnosis of nonallergic hypersensitivity is reserved for cases in which an immunologic mechanism is not proven.^{19,20} The six nonserious events of urticaria that were assessed as related to treatment were unlikely to be IgE-mediated and may have been due to another immunologic mechanism. However, an immunologic process seemed unlikely because the patient tolerated an IV formulation of C1-INH that contained the same active C1-INH protein and excipients as C1-INH (SC) (Berinert; CSL Behring) without incident before and after the study. In addition, the events occurred the day after administration of C1-INH (SC) rather than immediately after the injections. The urticaria events were assessed as a generalized hypersensitivity reaction that involved the skin.

CONCLUSION

C1-INH (SC) is a novel SC prophylactic treatment for the prevention of HAE attacks that has been shown to be effective, safe, and well tolerated.¹³ The approved 60-IU/kg dose of C1-INH (SC) resulted in a significant reduction in the HAE attack rate and a reduction in the use of rescue medication.¹³ With C1-INH (SC), C1-INH functional activity and antigen concentrations increase in a dose-dependent manner, with no dose-dependent safety concerns. Local ISRs were the most common

AEs observed in the COMPACT trial, but all were nonserious; the majority resolved within 24 hours, and none led to treatment discontinuation. There were no cases of anaphylaxis. The favorable safety profile of C1-INH (SC) demonstrated by the COMPACT trial has now been further confirmed by long-term safety data from the open-label extension of the COMPACT trial (maximum exposure of 2.7 years; mean, 1.5 years) and was also supported by the first year of postmarketing pharmacovigilance data.

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