

Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks

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Background: Hereditary angioedema caused by C1 esterase inhibitor deficiency is a rare disorder.

Objective: To compare the efficacy of pasteurized C1 esterase inhibitor concentrate (Berinert, CSL Behring) at intravenous doses of 10 or 20 U/kg body weight with placebo in the treatment of single, acute abdominal or facial attacks in patients with hereditary angioedema.

Methods: This was a randomized, double-blind, placebo-controlled study in 125 patients with type I or II hereditary angioedema. The primary outcome was time from start of treatment to onset of symptom relief. Secondary outcomes were time to complete resolution, proportion of patients with worsened intensity of angioedema symptoms between 2 and

4 hours after treatment, and number of vomiting episodes within 4 hours.

Results: Median time to onset of relief was significantly shorter with C1 esterase inhibitor concentrate at a dose of 20 U/kg than with placebo (0.5 vs 1.5 hours; $P = .0025$), whereas with 10 U/kg, the time to onset of relief was only slightly shorter than with placebo (1.2 vs 1.5 hours; $P = .2731$). Compared with placebo, the reduction in time to onset of relief was greatest for severe attacks (0.5 vs 13.5 hours). The secondary outcomes consistently supported the efficacy of the 20 U/kg dose. C1 esterase inhibitor concentrate was safe and well tolerated. No seroconversions were observed for HIV, hepatitis virus, or human B19 virus. **Conclusion:** C1 esterase inhibitor concentrate given intravenously at a dose of 20 U/kg is an effective and safe treatment for acute abdominal and facial attacks in patients with hereditary angioedema, with a rapid onset of relief. (*J Allergy Clin Immunol* 2009;124:801-8.)

Key words: C1 inhibitor, C1-INH, C1 inhibitor deficiency, angioedema, hereditary angioedema, HAE

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Hereditary angioedema (HAE) is a rare disorder with 3 known forms (types I, II, and III). Whereas types I and II are characterized by quantitative and/or functional C1 esterase inhibitor (C1-INH) deficiency, type III is characterized by normal complement levels and may be caused by mutations in the factor XII gene.^{1,2} C1-INH is one of the control proteins that regulates vascular permeability for the complement system.³⁻⁵ By inhibiting components of the complement (specifically C1r and C1s), contact (factor XII and kallikrein), coagulation (factor XI and thrombin), and fibrinolytic (tissue-type plasminogen activator and fibrinolysin) systems, C1-INH regulates the generation of vasoactive peptides, of which bradykinin is considered the most important.^{3,6,7} The regulation of bradykinin is a key step in preventing the development of angioedema.^{8,9} In type I HAE, impaired synthesis of functionally active C1-INH and elevated turnover result in insufficient plasma concentrations of C1-INH, whereas in type II HAE, a dysfunctional C1-INH molecule is synthesized in normal amounts.¹⁰ Except for 1 homozygous family,¹¹ both defects are inherited as an autosomal-dominant trait.¹²

The clinical manifestations of type I or II HAE are episodic bouts of well circumscribed, non-itching swelling of the deep cutaneous, subcutaneous, submucosal, and subepithelial tissues.^{12,13} Patients may experience swelling of the abdomen, face, genitalia, and extremities, abdominal pain, nausea, vomiting, or diarrhea, as well as life-threatening swelling of the larynx.¹⁴

Therapeutic options that are effective for histamine-induced angioedema, such as corticosteroids, antihistamines, or epinephrine,

Abbreviations used

C1-INH: C1 esterase inhibitor
HAE: Hereditary angioedema

have no effect on the pathophysiology of an acute HAE attack.^{6,15} Current treatment options in the United States for an acute type I or II HAE attack include fresh frozen plasma and ϵ -amino-caproic acid, which have variable efficacy and are associated with significant side effects.¹⁶ Outside the United States, the treatment of choice for an acute type I or II HAE attack is rapid replacement of the missing functional plasma protein C1-INH.¹⁷⁻¹⁹

Beriner (CSL Behring, Marburg, Germany) is a highly purified, virus-inactivated C1-INH concentrate²⁰ that is derived from human plasma collected in the United States. It is approved for the treatment of acute HAE attacks in several European and South American countries as well as in Japan; altogether, more than 400,000 treatments have been administered in more than 30 years of use. Approval is currently being sought for marketing in the United States (orphan drug designation).

To date, there is insufficient information from placebo-controlled studies to establish the effective dose of C1-INH concentrate in the treatment of acute HAE attacks. C1-INH was reported as being effective in the treatment of acute attacks in an earlier and smaller double-blind, placebo-controlled study with doses of 23 to 39 U/kg,²¹ and in an earlier uncontrolled study (not published) with doses equivalent to 6 to 15 U/kg body weight. Thus, we designed the current study (I.M.P.A.C.T.1) to assess the efficacy and safety of C1-INH (Beriner) at a dose of 20 U/kg, compared with placebo. A secondary objective was to evaluate the efficacy of a lower dose of 10 U/kg.

METHODS

Study design

This multinational, parallel-group, randomized, placebo-controlled, 3-arm, double-blind, phase II/III study (with a dose-finding substudy) was conducted between August 2005 and December 2007. Our aim was to show that C1-INH shortens the time to onset of symptom relief in acute abdominal or facial HAE attacks compared with placebo and to provide a statistically secure dosing recommendation for C1-INH.

The independent ethics committee or institutional review board at each participating center approved the protocol, and written informed consent was obtained from each patient or, in the case of a minor, from a legally acceptable representative. An independent data and safety monitoring board oversaw the safety of the study.

Patients were eligible if they were at least 6 years of age and had laboratory-confirmed C1-INH deficiency (type I or II HAE) and were then treated on presentation of an acute moderate to severe abdominal or facial attack within 5 hours of the attack attaining moderate intensity (as assessed by the patient and confirmed by the investigator).

Relevant exclusion criteria included history of hypersensitivity to C1-INH concentrates, acquired angioedema, all other types of angioedema and abdominal pain not associated with C1-INH deficiency, habitual use of narcotics or use of pain medication during a current attack, and treatment with any C1-INH concentrate or other drug appropriate for acute angioedema, or with fresh frozen or native plasma, within 7 days before the start of treatment.

Randomization was performed by using a centralized, validated computerized system that assigned a unique patient number to each participant.

For each patient, only a single abdominal attack (gastrointestinal colic, not cutaneous) or facial attack (not laryngeal) was treated and evaluated. Patients received a single intravenous infusion of either C1-INH (Beriner) at a dose of 10 or 20 U/kg, or placebo. In addition to the usual precautions, the double-blinding was considered to have been maintained because the volume and

appearance of all 3 treatments were identical, and there were no dose-related local or systemic reactions associated with the treatments.

Patients were observed for a minimum of 4 hours after the start of treatment, after which they could be discharged from the center if they had reported onset of symptom relief. After 4 hours, patients who reported insufficient or no symptom relief could receive a second dose of double-blind treatment (called "rescue study medication") as follows: C1-INH 20 U/kg for patients on placebo, C1-INH 10 U/kg for patients on C1-INH 10 U/kg, and placebo for patients on C1-INH 20 U/kg. A viral safety assessment was performed before and for as long as 12 weeks after treatment.

Study outcomes

The primary endpoint was the time from the start of treatment to the onset of symptom relief, as determined by patient responses to a standard question posed at appropriate time intervals for as long as 24 hours after the start of treatment. To provide a stringent analysis, the time to onset of symptom relief was set at 24 hours if a patient received rescue study medication before the onset of relief, or received analgesics, antiemetics, or open-label C1-INH or fresh frozen plasma during the first 4 hours after treatment.

This type of endpoint has been widely reported in the scientific literature for the evaluation of HAE therapies (eg, Waytes et al,¹⁷ Kunschak et al,²¹ and subsequent studies summarized by Frank²²) and is also accepted by regulators in the United States and Europe.^{23,24} In addition, we retrospectively validated the primary endpoint by correlation with the course of the associated HAE symptoms (data on file). Secondary endpoints were the time to complete resolution of all HAE symptoms, the proportion of patients with worsened intensity of HAE symptoms between 2 and 4 hours after the start of treatment compared with baseline for at least 1 HAE symptom present at baseline, and the number of vomiting episodes within 4 hours after the start of treatment.

Other data captured included adverse events occurring as long as 9 days after treatment (serious adverse events as long as 12 weeks after treatment), vital signs (blood pressure, heart and respiratory rate, body temperature) before and as long as 24 hours after treatment, and viral safety (HIV types 1 and 2, hepatitis virus, and human B19 virus) before and as long as 12 weeks after treatment.

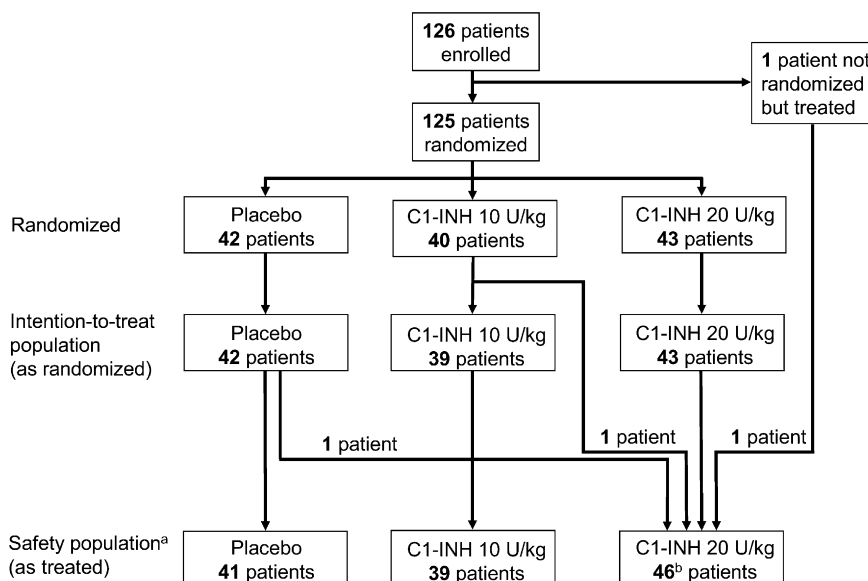
Statistical analysis

The planned sample size was 42 patients per treatment group, which was the maximum feasible number in this rare disease. Efficacy analyses were based on the intention-to-treat principle and included all patients who received any blind study treatment. The patients were analyzed according to the treatment group to which they were randomized.

The primary variable, time to onset of symptom relief for C1-INH 20 U/kg versus placebo, was evaluated using a Wilcoxon 1-sided, 2-sample test. A confirmatory test was used for the primary analysis with a maximum allowed type I error of 0.025, 1-sided, in a group sequential design with a nominal α at final analysis of 0.024. Because there were only 2 groups, no α correction for multiple testing was necessary; instead, only a small α correction for sequential testing was needed. For the secondary objective of dose-finding, a 2-step closed testing procedure with Wilcoxon 2-sample tests was used with a maximum allowed type I error of 0.05, 1-sided.^{25,26}

The secondary efficacy variables of number of vomiting episodes and time to complete resolution of symptoms were also evaluated by using the Wilcoxon 1-sided 2-sample test. A 1-sided Fisher exact test was used for the secondary efficacy variable of worsened intensity of symptoms between 2 and 4 hours after the start of treatment. For all secondary efficacy variables (except time to complete resolution of all symptoms, which was considered an exploratory variable), confirmatory tests with a maximum allowed type I error of 0.1, 1-sided, were carried out. In addition, we conducted efficacy analyses with a stratified nonparametric Brunner test²⁷ to investigate the onset of symptom relief stratified by type and intensity of baseline attack.

Safety data were analyzed for all patients who had received any treatment, according to the actual treatment received. An analysis of adverse events occurring within 4 hours after treatment was conducted to allow an unbiased comparison of C1-INH 20 U/kg versus placebo during maximum exposure to treatment in the acute phase of the attack (ie, without the confounding effect of any rescue medication). In addition, adverse events were analyzed for all



125 patients were randomized at 36 centers worldwide (Australia, Argentina, Bulgaria, Canada, Czech Republic, Great Britain, Hungary, Israel, Republic of Macedonia, Poland, Romania, Russia, Spain, Sweden, and United States).

^a Safety population status at 4 hours after treatment.

^b In addition to the 43 patients randomized to C1-INH 20 U/kg, 3 further patients also ended up being treated with C1-INH 20 U/kg and were therefore included in this group for the safety analysis. One patient randomized to placebo experienced an abdominal attack within 4 hours of the randomized treatment and was treated with C1-INH 20 U/kg as (blind) rescue study medication. One patient randomized to C1-INH 10 U/kg experienced a laryngeal attack before the planned treatment with C1-INH 10 U/kg, and instead received C1-INH 20 U/kg as open-label rescue medication. One patient had an abdominal attack that was erroneously treated with C1-INH 20 U/kg without first having been formally randomized; this patient was not analyzed for efficacy, but was included in the C1-INH 20 U/kg group for the safety analysis.

FIG 1. Patient disposition by treatment group.

patients who received any C1-INH at any time during the study, including patients in the placebo group who received C1-INH as rescue medication. Incidence rates were calculated by system organ class, preferred term, and dose group. No routine laboratory data were obtained. Vital signs and viral safety data were analyzed descriptively.

The sponsor's clinical research department was responsible for designing and conducting the study, approving the statistical plan, and gathering and reporting the data. The statistical analyses were conducted by Accovion GmbH, Marburg, Germany, which vouches for the data and the analysis. The results of the study were interpreted and discussed by the named authors at a series of scientific meetings during the development of this article. The sponsor (represented by P. C. Kiessling) took the lead in writing this article and coordinated writing of the article with the named authors; the sponsor also engaged a consultant medical writer to assist with preparation of the first draft in cooperation with the named authors. The sponsor placed no restrictions on any of the authors regarding statements made in the article.

RESULTS

Study population

We randomized 125 patients at 36 centers worldwide to receive double-blind treatment, of whom 42 were assigned to receive

placebo, 40 to receive C1-INH 10 U/kg, and 43 to receive C1-INH 20 U/kg (Fig 1).

The treatment groups were similar in terms of sex, age, and race or ethnic group (Table I). Most patients (87.1%) had type 1 HAE. Danazol was taken during the study by 14 (11.3%) patients. Overall, 98 (79.0%) patients experienced abdominal attacks, and 25 (20.2%) experienced facial attacks. One randomized patient was excluded from the intention-to-treat population because of the need for open-label rescue medication before receiving the randomized treatment (Fig 1).

The percentage of patients who received rescue study medication was considerably higher with placebo (57.1%) than with C1-INH 10 U/kg (33.3%) or 20 U/kg (18.6%).

Efficacy outcomes

For the primary efficacy analysis, the time to onset of symptom relief was set to 24 hours if the patient received rescue study medication or analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma after 4 hours. The numbers of patients with values

TABLE I. Demographic and baseline characteristics (intention-to-treat population)

Characteristic	Placebo (N = 42)	C1-INH 10 U/kg (N = 39)	C1-INH 20 U/kg (N = 43)	Overall (N = 124)
Sex, n (%)				
Female	28 (66.7)	26 (66.7)	30 (69.8)	84 (67.7)
Male	14 (33.3)	13 (33.3)	13 (30.2)	40 (32.3)
Age (y)				
Mean (SD)	31.5 (13.57)	33.1 (12.77)	34.6 (14.91)	33.1 (13.76)
Range	6-62	13-72	10-71	6-72
Race or ethnic group, n (%)				
White	37 (88.1)	36 (92.3)	38 (88.4)	111 (89.5)
Black	1 (2.4)	0	3 (7.0)	4 (3.2)
Hispanic	1 (2.4)	2 (5.1)	2 (4.7)	5 (4.0)
Asian	2 (4.8)	1 (2.6)	0	3 (2.4)
American Indian or Alaskan Native	1 (2.4)	0	0	1 (0.8)
BMI (kg/m ²)				
Mean (SD)	25.3 (6.00)	26.7 (5.29)	27.0 (5.57)	26.4 (5.64)
Range	13-38	17-36	18-40	13-40
Primary disease characteristic, n (%)				
Type I HAE	38 (90.5)	35 (89.7)	35 (81.4)	108 (87.1)
Type II HAE	4 (9.5)	3 (7.7)	8 (18.6)	15 (12.1)
Missing	—	1 (2.6)	—	1 (0.8)
Intensity of baseline HAE attack, n (%)				
Moderate	26 (61.9)	32 (82.1)	27 (62.8)	85 (68.5)
Severe	16 (38.1)	7 (17.9)	16 (37.2)	39 (31.5)

BMI, Body mass index.

TABLE II. Results of primary and secondary efficacy analyses (intention-to-treat population)

Statistic	Placebo (N = 42)	C1-INH 10 U/kg (N = 39)	C1-INH 20 U/kg (N = 43)	P value 20 U/kg – placebo
Time to onset of symptom relief (h), primary efficacy analysis*				
Mean (SD)	10.27 (11.481)	7.47 (10.513)	3.89 (8.202)	
Median (range)	1.50 (0.20-24.00)	1.17 (0.17-24.00)	0.50 (0.17-24.00)	.0025†(.0078‡)
Time to complete resolution of all HAE symptoms, including pain (h)§				
Mean (SD)	125.08 (382.815)	216.06 (494.230)	81.84 (314.347)	
Median (range)	7.79 (0.33-1486.17)	20.00 (0.47-1486.17)	4.92 (0.47-1486.17)	.0237
Proportion of patients with worsened intensity of HAE symptoms between 2 and 4 hours after start of treatment				
N (%)	13 (31.0)	8 (20.5)	2 (4.7)	.0014¶
No. of vomiting episodes within 4 hours after start of treatment				
Mean (SD)	0.8 (2.59)	0.2 (0.77)	0.1 (0.41)	
Median (range)	0 (0-16)	0 (0-4)	0 (0-2)	.0329†

*Time to onset of symptom relief was set to 24 hours if the patient received rescue study medication or analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma after 4 hours. The numbers of patients with values set to 24 hours were as follows: placebo, 17/42 (40.5%); C1-INH 10 U/kg, 11/39 (28.2%); C1-INH 20 U/kg, 6/43 (14.0%).

†One-sided 2-sample Wilcoxon test.

‡Exploratory 2-sided log-rank test.

§Irrespective of use of rescue study medication or analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma before onset of symptom relief. Missing values were set to maximum time to complete resolution (ie, 1486 hours).

||Exploratory 1-sided 2-sample Wilcoxon test.

¶One-sided Fisher exact test.

set to 24 hours were 17 of 42 (40.5%) for placebo, 11 of 39 (28.2%) for C1-INH 10 U/kg, and 6 of 43 (14.0%) for C1-INH 20 U/kg. In this stringent analysis, the median time to onset of symptom relief was significantly shorter with C1-INH 20 U/kg (0.5 hours) than with placebo (1.5 hours; $P = .0025$; Table II). With C1-INH 10 U/kg, the median time to onset of symptom relief was only slightly shorter than with placebo (1.2 hours vs 1.5 hours). One hour after treatment, more than 75% of patients treated with C1-INH 20 U/kg had reported onset of symptom relief, compared with approximately 40% of patients treated with placebo (Fig 2, A). Using a closed testing procedure for dose finding, the comparison of time to onset of symptom relief revealed statistical significance for

C1-INH 20 U/kg versus 10 U/kg ($P = .0048$), and no statistical significance for C1-INH 10 U/kg versus placebo ($P = .2731$).

The median time to onset of symptom relief was relatively short for abdominal attacks (placebo, 1.3 hours; C1-INH 10 U/kg, 1.2 hours; C1-INH 20 U/kg, 0.5 hours) compared with facial attacks (placebo, 24.0 hours; C1-INH 10 U/kg, 1.3 hours; C1-INH 20 U/kg, 0.9 hours; Table III). However, the stratified analysis could not confirm any difference in treatment effect between facial and abdominal attacks (data not shown). The treatment effect was described as an estimated probability in terms of the time to onset of symptom relief for a patient receiving C1-INH 20 U/kg being shorter than the respective time for a patient receiving placebo.

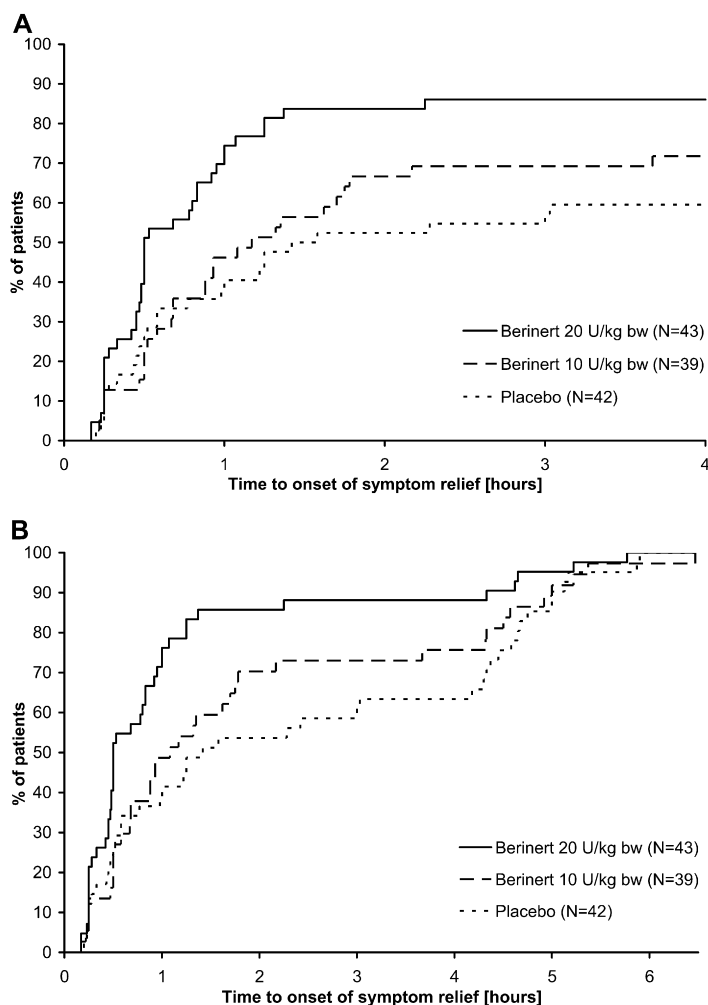


FIG 2. Kaplan-Meier curves for time to onset of symptom relief, as determined by patient assessment (intention-to-treat population). **A**, Values set to 24 hours if rescue medication was given before onset of symptom relief (primary analysis). Only the curves for as long as 4 hours after treatment are shown because values did not change thereafter through 24 hours after treatment. **B**, Actual values recorded (ie, values not set to 24 hours if rescue medication was given before onset of symptom relief). *BW*, Body weight.

Although the median time to onset of symptom relief was more pronounced for severe attacks (placebo, 13.5 hours; C1-INH 20 U/kg, 0.5 hours) than for moderate attacks (placebo, 1.3 hours; C1-INH 20 U/kg, 0.8 hours; [Table III](#)), a 2-sided test for interaction could not confirm any difference in treatment effect between moderate and severe attacks ($P = .463$). In both cases, the efficacy compared with placebo was greater with C1-INH 20 U/kg than with C1-INH 10 U/kg.

The results of the secondary efficacy analyses generally supported the results of the primary analysis ([Table II](#)). The median time to complete resolution of HAE symptoms was significantly lower with C1-INH 20 U/kg (4.9 hours) than with placebo (7.8 hours; $P = .0237$). Compared with placebo, the median time to complete resolution of HAE symptoms was longer for the 10 U/kg group, which can be attributed to the confounding effect of rescue study medication.

The proportion of patients with worsened intensity of HAE symptoms between 2 and 4 hours after the start of treatment for at least 1 of the HAE symptoms present at baseline was also

significantly lower with C1-INH 20 U/kg (4.7%) than with placebo (31.0%; $P = .0014$). The mean number of vomiting episodes within the first 4 hours after treatment was also significantly lower with C1-INH 20 U/kg (0.1) than with placebo (0.8; $P = .0329$).

The treatment effect with C1-INH 10 U/kg was less than with C1-INH 20 U/kg, but greater than with placebo, for the primary efficacy analysis as well as for the secondary efficacy analyses of the proportion of patients with worsened intensity of clinical symptoms and number of vomiting episodes ([Table II](#)).

In patients with abdominal or facial attacks treated with C1-INH 20 U/kg, no new attacks occurred before the complete resolution of the previous attack, indicating an absence of rebound angioedema. One patient in this group had a missing value for the time to complete resolution of 1 attack, but the next attack in this patient occurred 7 days later. Because the median elimination half-life of C1-INH is approximately 35 hours,²⁸ this subsequent attack cannot reflect any ineffective treatment of the earlier attack.

TABLE III. Analyses of time to onset of symptom relief by HAE attack characteristics (intention-to-treat population)

Characteristic	Statistic	Time to onset of symptom relief (h)*		
		Placebo (N = 42)	C1-INH 10 U/kg (N = 39)	C1-INH 20 U/kg (N = 43)
Type of attack†				
Abdominal	N	33	31	34
	Mean (SD)	8.59 (11.083)	7.59 (10.680)	3.37 (7.659)
	Median (range)	1.25 (0.20-24.00)	1.17 (0.17-24.00)	0.50 (0.17-24.00)
Facial	N	8	8	9
	Mean (SD)	15.47 (11.802)	7.02 (10.531)	5.89 (10.274)
	Median (range)	24.00 (0.25-24.00)	1.32 (0.50-24.00)	0.92 (0.25-24.00)
Intensity of attack‡				
Moderate	N	26	32	27
	Mean (SD)	8.92 (11.204)	8.12 (10.885)	4.95 (9.259)
	Median (range)	1.33 (0.25-24.00)	1.13 (0.22-24.00)	0.78 (0.17-24.00)
Severe	N	16	7	16
	Mean (SD)	12.44 (11.953)	4.50 (8.682)	2.11 (5.862)
	Median (range)	13.50 (0.20-24.00)	1.35 (0.17-24.00)	0.50 (0.17-24.00)

*Time to onset of symptom relief was set to 24 hours if the patient received rescue study medication or analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma after 4 hours.

†One patient was originally randomized with a facial attack, which was later reassessed as a laryngeal attack.

‡Assessment of intensity of symptoms of the HAE attack: the intensity (mild, moderate, or severe) was stated by the patient and confirmed by the investigator. Only patients with moderate to severe HAE attacks were to be included in the study.

TABLE IV. Incidence of adverse events (safety population)

Adverse event category	No. (%) of patients			
	As long as 4 hours after treatment			Any time C1-INH All doses* (N = 108)
	Placebo (N = 41)	C1-INH 10 U/kg (N = 39)	C1-INH 20 U/kg (N = 46)	
Patients with adverse events	18 (43.9)	10 (25.6)	9 (19.6)	55 (50.9)
Patients with at least possibly related adverse events	8 (19.5)	8 (20.5)	5 (10.9)	29 (26.9)
Patients with serious adverse events	0	0	0	4 (3.7)
Patients with adverse events leading to discontinuation of treatment	0	0	0	0
Most common adverse events (>1 patient overall)				
Hereditary angioedema	0	0	0	14 (13.0)
Headache	2 (4.9)	1 (2.6)	0	13 (12.0)
Abdominal pain	3 (7.3)	1 (2.6)	2 (4.3)	7 (6.5)
Nausea	5 (12.2)	1 (2.6)	3 (6.5)	7 (6.5)
Muscle spasms	2 (4.9)	4 (10.3)	1 (2.2)	6 (5.6)
Pain	1 (2.4)	4 (10.3)	1 (2.2)	6 (5.6)
Diarrhea	4 (9.8)	1 (2.6)	0	5 (4.6)
Vomiting	3 (7.3)	1 (2.6)	1 (2.2)	5 (4.6)
Back pain	1 (2.4)	0	0	4 (3.7)
Dysgeusia	0	1 (2.6)	2 (4.3)	4 (3.7)
Edema peripheral	0	1 (2.6)	1 (2.2)	4 (3.7)
Abdominal distension	0	1 (2.6)	0	2 (1.9)
Upper respiratory tract infection	0	0	0	2 (1.9)
Face edema	1 (2.4)	1 (2.6)	0	1 (0.9)
Lip swelling	1 (2.4)	1 (2.6)	0	1 (0.9)

*Patients treated with C1-INH at any time during the study, including use of C1-INH as rescue medication in the placebo and C1-INH 10 U/kg groups.

Safety and tolerability

A total of 126 patients (placebo, 41 patients; C1-INH 10 U/kg, 39 patients; C1-INH 20 U/kg, 46 patients) were included in the safety population (Fig 1).

The percentage of patients experiencing an adverse event within 4 hours after start of treatment was considerably lower with C1-INH 20 U/kg (19.6%) than with placebo (43.9%; Table IV). Adverse events considered at least possibly related to treatment were also less frequent with C1-INH 20 U/kg (10.9%) than with placebo (19.5%). Most patients reported events in the system organ classes of gastrointestinal disorders,

general disorders and administration site conditions, and musculoskeletal and connective tissue disorders, with lower percentages among patients treated with C1-INH 20 U/kg than with placebo for all these categories. The difference between C1-INH 20 U/kg and placebo was particularly pronounced for gastrointestinal disorders (10.9% vs 31.7%), which was expected because most patients experienced abdominal HAE attacks. The most frequent events were nausea, diarrhea, abdominal pain, and muscle spasms, and the frequencies of all these events were lower with C1-INH 20 U/kg than with placebo. Most of these symptoms are related to the underlying

disease and type of attack. With C1-INH 10 U/kg, the percentage of patients with an adverse event (25.6%) was also considerably lower than with placebo (43.9%).

No serious adverse events or adverse events leading to discontinuation of treatment occurred within 4 hours after study treatment. Later in the study, 4 patients had 9 serious adverse events of HAE exacerbation. One of these events was considered at least possibly related to treatment, and this event occurred in the 1 patient whose diagnosis of HAE was questioned after genetic testing. The vital signs measurements revealed no signals of concern.

Virus safety

No seroconversions were observed for HIV, hepatitis virus, or human B19 virus.

DISCUSSION

C1 esterase inhibitor concentrate has been in clinical use for treating acute type I and II HAE attacks since 1979. Most information on this use is based on observational studies, which have consistently reported beneficial efficacy and safety of C1-INH when treating acute HAE attacks in adults and children.²⁹⁻³⁴ None of these studies had a randomized, placebo-controlled design to evaluate the most suitable dose of C1-INH. To address this issue, we conducted a double-blind, placebo-controlled study in patients with type I and II HAE, in which single acute HAE attacks were treated with C1-INH 10 or 20 U/kg, or placebo. The findings demonstrated consistent and statistically significant efficacy of C1-INH 20 U/kg compared with placebo across all efficacy endpoints.

The primary efficacy analysis demonstrated that C1-INH 20 U/kg provides fast onset of symptom relief within 30 minutes, with a significant reduction in time to onset of relief compared with placebo ($P = .0025$). In terms of dose-finding, the comparison of time to onset of relief revealed statistical significance for C1-INH 20 U/kg versus 10 U/kg ($P = .0048$) and no statistical significance for C1-INH 10 U/kg versus placebo ($P = .2731$).

No difference in treatment effect in terms of time to onset of symptom relief could be confirmed by stratified analysis when comparing the efficacy of C1-INH 20 U/kg in facial and abdominal attacks, and in moderate and severe attacks. Therefore, C1-INH 20 U/kg may be considered efficacious irrespective of the body location studied (facial or abdominal sites) or the severity of an attack. This finding is clinically relevant because HAE is a debilitating disease, and patients with frequent attacks have severe impairment in their quality of life. Further evidence for the convincing efficacy of C1-INH 20 U/kg lies with the lack of any new attack having occurred in this treatment group before complete resolution of the previous attack, indicating an absence of rebound angioedema.

The fact that C1-INH 10 U/kg did not show statistically significant efficacy compared with placebo in our study, in contrast with published data indicating the efficacy of this dose or lower (eg, 500 U per attack, approximately 7 U/kg),²⁹⁻³⁴ reflects the more stringent criteria used for defining efficacy endpoints in the confines of our double-blind, placebo-controlled study.

The safety analyses revealed no signals of concern, confirming the favorable safety profile of C1-INH reported

previously.^{8,30,32,33,35,36} A concern when administering plasma-derived products is the potential risk for virus transmission to recipients. During our study, consistent with 30 years of post-marketing surveillance data, there were no proven virus seroconversions with C1-INH.^{30,32} Therefore, we conclude that the potential risk for viral transmission with the use of C1-INH is minimal.

Our results show that C1-INH 20 U/kg administered intravenously is a reliable and effective treatment for rapidly alleviating symptoms of abdominal and facial HAE attacks. Efficacy of the lower C1-INH dose of 10 U/kg was not statistically significant compared with placebo. The recommended dose of C1-INH concentrate in the treatment of acute HAE attacks is therefore 20 U/kg. Taken together, these data address the acknowledged need for double-blind, placebo-controlled studies to assess appropriate doses of novel therapies being investigated for the treatment of HAE.¹⁴ C1-INH provides an important contribution to the currently limited range of options for treating acute attacks in type I or II HAE.

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Clinical implications: C1 esterase inhibitor at a dose of 20 U/kg is a reliable and effective treatment for rapidly alleviating symptoms of HAE attacks, irrespective of body location or severity.

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