

Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema

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Background: Hereditary angioedema (HAE) results from a genetic deficiency of C1-inhibitor. Two similar independent, randomized, saline controlled, double-blind studies were conducted to evaluate the efficacy and safety of recombinant human C1-inhibitor (rhC1INH) as a treatment of acute angioedema attacks in patients with HAE.

Objective: Analysis of pooled study results.

Methods: Patients with an eligible attack were randomized to a single intravenous dose of rhC1INH or saline. Efficacy was assessed by using patient-reported visual analog scale outcomes, and safety was assessed by using adverse events and immunogenicity of rhC1INH.

Results: rhC1INH at 100 (n = 29) and 50 (n = 12) U/kg body weight resulted in a significant reduction for both the primary endpoint time to the beginning of relief of symptoms compared with saline (n = 29): median, 66 (95% CI, 61-122) minutes, 122 (72-136) minutes, and 495 (245-520) minutes, $P < .001$ and $P = .013$, respectively; and for the secondary endpoint time to minimal symptoms, median, 266 (242-490) minutes, 247 (243-484) minutes, and 1210 (970-1500) minutes, $P < .001$ and $P = .001$, respectively. Therapeutic failure occurred in 59% (17/29) of the saline group compared with 0% (0/12) of the 50 U/kg group and 10% (3/29) of the 100 U/kg group. Treatment-emergent adverse events were unremarkable and tended to be reported more frequently in the saline group. No postexposure antibody responses against rhC1INH or host-related impurities were observed.

Conclusion: Administration of rhC1INH at 100 or 50 U/kg was highly effective as a treatment of acute attacks in patients with HAE and appeared to be safe and well tolerated. (J Allergy Clin Immunol 2010;126:821-7.)

Key words: HAE, angioedema, attack, recombinant human C1-inhibitor, efficacy, safety

Hereditary angioedema (HAE) results from a heterozygous deficiency of the plasma protein C1-inhibitor (C1INH) and has a prevalence of 1 in 50,000.¹ Mutations of the C1INH gene^{2,3} result in type I HAE with low functional and protein levels of C1INH, or type II HAE with low functional and normal protein levels of C1INH. The clinical presentations of type I and type II HAE are similar.^{4,5}

Patients with HAE experience acute attacks of angioedema in subcutaneous or submucosal soft tissues, which may occur less than once per year to several times per month.^{2,4,6,7} Typically, untreated attacks last for 1 to 5 days. Swellings can be located in the extremities, larynx, pharynx, face, abdomen, and genitalia. Angioedema formation in the upper airways may involve the vocal cords and the larynx and can lead to death by asphyxiation.^{8,9} Abdominal attacks may cause severe pain, nausea, vomiting, and diarrhea, whereas attacks in the extremities, face, and genitalia are disfiguring and interfere with activities of daily living.

Uncontrolled activation of complement and contact pathways leading to the episodic formation of vasoactive peptides, such as bradykinin, presumably cause angioedema,^{10,11} which can be effectively treated by replacement therapy with C1INH.¹²⁻¹⁵

Recombinant human C1INH (rhC1INH) is expressed in the milk of transgenic rabbits.¹⁶ In open-label trials, rhC1INH appeared to be safe and effective in the treatment of acute attacks in patients with HAE.¹⁷⁻¹⁹ Here we report the pooled results of 2 randomized, saline-controlled, double-blind trials evaluating rhC1INH in the treatment of acute HAE attacks.

METHODS

Study design

C1 1205-01 and C1 1304-01 were 2 independent, randomized, saline-controlled, double-blind studies to evaluate the efficacy and clinical and laboratory safety of rhC1INH in the treatment of acute angioedema attacks in patients with HAE. The studies were similar in design, entry criteria, and endpoints. Study C1 1205-01 (clinicaltrials.gov identifier: NCT00225147) was conducted in 26 US and 4 Canadian centers ("North American"). Study C1 1304-01 (clinicaltrials.gov identifier: NCT00262301) was conducted in 11 centers in Italy, Spain, Romania, the United Kingdom, and Israel ("European"), and both were conducted in compliance with the Declaration of Helsinki and national regulatory provisions. The study protocols were approved by the ethical committee or institutional review board at each center. Each study was monitored by an independent data and safety monitoring committee.

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Abbreviations used

AE:	Adverse event
C1INH:	C1-inhibitor
CI:	Confidence intervals
Cox PH:	Cox proportional hazards
HAE:	Hereditary angioedema
rhC1INH:	Recombinant human C1INH
TEAE:	Treatment-emergent adverse event
VAS:	Visual analog scale

Inclusion criteria were age (12 years or older in the North American study, 16 years or older in the European study), signed informed consent, and functional C1INH in plasma <50% of normal.²⁰ Exclusion criteria included a history of allergy against rabbits and acquired C1INH deficiency. Patients were eligible for randomization on presenting with onset of attack symptoms <5 hours and an overall severity visual analog scale (VAS) score (see Clinical Evaluation below) ≥50 mm. Exclusion criteria for randomization included use of narcotics or antiemetics. Any patient included in the studies progressing to a life-threatening attack after inclusion was withdrawn from the study and treated with rescue medication such as plasma-derived C1INH. For details of inclusion and exclusion criteria, see this article's [Tables E1 and E2](#) in the Online Repository at www.jacionline.org.

Patients with an eligible attack were randomized equally (1:1:1) to receive intravenously 100 or 50 U/kg rhC1INH or saline in the North American study, or (1:1) to receive 100 U/kg rhC1INH or saline in the European study. One unit of C1INH is defined as the amount in 1 mL pooled normal human plasma.

Clinical evaluation

Efficacy of therapeutic interventions in HAE attacks was assessed by using a patient-reported outcome VAS score.²¹ To permit consistent evaluation of treatment outcome at different anatomical locations, patients were asked to mark the overall severity of angioedema symptoms on a continuous scale from 0 to 100 mm, with 0 mm meaning "no symptoms at all" and 100 mm meaning "extremely disabling." This score was recorded at the time of evaluation (–1 hour), at the start of infusion (baseline), and at various times thereafter (see this article's [Table E3](#) in the Online Repository at www.jacionline.org) for any of 4 anatomical locations—abdominal, genitourinary, oro-facial-pharyngeal-laryngeal region, or peripheral—at which symptoms were present.

Study outcomes

The primary efficacy endpoint was the time to the beginning of relief of symptoms—that is, the interval during which the VAS score at any eligible location had decreased by ≥20 mm compared with baseline for 2 consecutive VAS recordings. The secondary efficacy endpoint was the time to minimal symptoms—that is, the interval during which the VAS score had decreased to <20 mm for all anatomical locations of an attack. Changes of 20 mm on 100-mm VAS scales are considered to represent significant clinical changes (J. Speight, unpublished data, 2009; L. Kaufman, unpublished data, 2009).^{22,23} Treatment outcome was also assessed for therapeutic failure (see this article's [Table E4](#) in the Online Repository at www.jacionline.org).

The primary safety outcome was the occurrence of treatment-emergent adverse events (TEAEs), which were adverse events (AEs) from time of administration of study medication until 90 days thereafter. TEAEs were coded by using the Medical Dictionary for Regulatory Activities. Safety evaluation also included assessment of vital signs, electrocardiogram, physical examination, laboratory parameters and immunogenicity testing.

Laboratory methods

Hematologic and biochemical parameters were determined by using routine clinical assays. Functional C1INH activity was assessed with a chromogenic assay²⁰ and expressed as a percentage of normal. Protein levels of C1INH and C4 were measured with nephelometric assays and C1q with ELISA.

Antibodies against C1INH of IgM, IgG, and IgA classes were measured in plasma samples obtained before and for up to 90 days after administration of rhC1INH by using ELISAs with rhC1INH and plasma-derived C1INH as antigens. Antibodies against impurities arising from the transgenic rabbit milk were measured with an ELISA with rabbit milk proteins as antigen.

Statistical analysis

All patients who received study medication were included in the analysis. Data were analyzed by using the SAS system version 9.1.3 (SAS Institute, Cary, NC).

Patients who did not have beginning of relief of symptoms or minimal symptoms during the observation time were censored at the time of the last overall VAS score for the eligible locations.

Time to event data are given as median time with 95% CIs and depicted as Kaplan-Meier plots. These data were analyzed by using a Cox proportional hazards (Cox PH) model with study and study medication group included as covariates. Cox regression was used to calculate hazard ratios with 95% CI and associated 2-sided *P* value for rhC1INH versus saline dose groups. The number of patients with therapeutic failure in the treatment groups was compared by using an exact logistic regression model that included study as a covariate and dose group as a factor. Data are presented as the odds ratios with 95% CIs comparing rhC1INH treatment groups versus saline. No adjustment for multiplicity was performed for the various analyzed variables because a primary and a single secondary variable were defined prospectively in the protocol. Treatment groups were compared according to a hierarchical closed test procedure in which initially the rhC1INH (100 U/kg) and saline groups were compared. When a *P* value ≤0.05 was found, the rhC1INH (50 U/kg) and saline groups were also compared.

RESULTS

Patients included

Overall, 290 patients with HAE were found to be eligible on screening ([Fig 1](#)). Seventy of these patients, 32 patients in the European study and 38 in the North American study, presented with an eligible attack and were randomized. Randomized treated patients were comparable with the nontreated eligible patients (see this article's [Table E5](#) in the Online Repository at www.jacionline.org). The majority of nontreated eligible patients did not receive treatment because they did not present with an eligible attack.

The randomized, double-blind, saline-controlled phases of both the North American study and the European study were closed after interim analyses and on the advice of the respective independent data monitoring committees because of compelling statistically significant positive efficacy findings and no apparent adverse safety findings.

In the European study, 34 HAE patients with an acute angioedema attack were randomized and 32 received treatment ([Fig 1](#)), 16 rhC1INH and 16 saline. Two patients were randomized to receive saline and rhC1INH, respectively, but were not treated, 1 because of spontaneous regression of the attack, another because of development of a potentially life-threatening attack. In the North American study, 39 patients were randomized and 38 received treatment ([Fig 1](#))—13 received 100 U/kg rhC1INH, 12 received 50 U/kg, and 13 received saline. One patient, randomized to receive 50 U/kg rhC1INH, was not treated because the overall severity VAS was <50 mm. Overall, 70 patients received randomized treatment with rhC1INH or saline. Treatment groups were comparable in demographics (see this article's [Table E6](#) in the Online Repository at www.jacionline.org), attack locations, pretreatment VAS scores, and complement parameters ([Table I](#)). On review, several patients' attacks did not meet all eligibility criteria ([Table I](#));

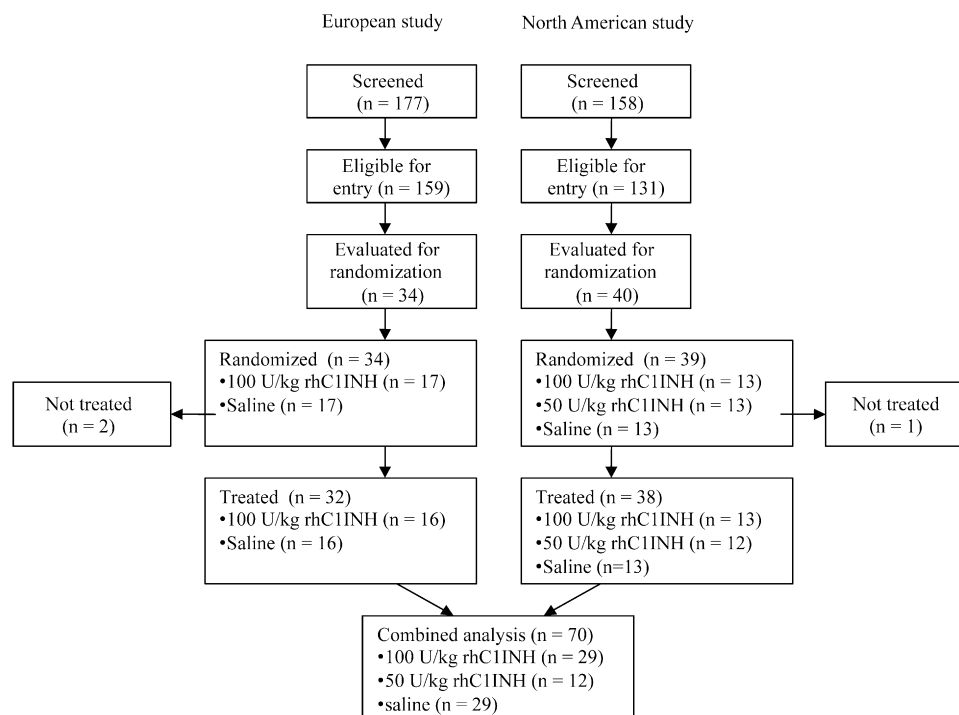


FIG 1. Inclusion of patients with HAE and eligible attacks by study.

however, they were included in the analyses because these were prespecified as intention-to-treat analyses. Sensitivity analyses on the per-protocol patient populations yielded similar results (data not shown). Eight patients did not complete the study follow-up to 90 days after treatment; 4 had an open-label treatment of a subsequent angioedema attack with rhC1INH before day 90 (see this article's Table E8 in the Online Repository at www.jacionline.org), and 4 were lost to follow-up. No patient was withdrawn from the studies because of development a life-threatening attack after administration of study drug.

Efficacy outcome

The mean overall VAS score of both rhC1INH groups decreased more rapidly than that of the saline group (Fig 2). Treatment with rhC1INH 100 (n = 29) and 50 (n = 12) U/kg achieved the primary endpoint with significant reduction in time to beginning of relief of symptoms, median, 66 (95% CI, 61-122) minutes, 122 (72-136) minutes, compared with saline (n = 29), 495 (245-520) minutes, $P < .001$ and $P = .013$, respectively (Table II, Fig 3; data broken down by study are given in this article's Table E9 in the Online Repository at www.jacionline.org). Treatment with rhC1INH 100 (n = 29) and 50 (n = 12) U/kg also resulted in a significant reduction of time to minimal symptoms, median, 266 (242-490) minutes and 247 (243-484) minutes, respectively, compared with treatment with saline, median, 1210 (970-1500) minutes, $P < .001$ and $P = .001$, respectively (Table II; Fig 3).

Fifty-nine percent (17/29) of the patients in the saline group had a therapeutic failure compared with 0% (0/12) in the 50 and 10% (3/29) in the 100 U/kg groups (see this article's Table E10 in the Online Repository at www.jacionline.org). Odds ratios (95% CI) for the dose groups versus the saline group were 0.06

(0.01-0.32) for the 100 U/kg group and 0.13 (0.00-1.08) for the 50 U/kg group, $P < .001$ and $P = .060$, respectively. The larger 95% CI of the odds ratios for the low-dose group (0/12 treatments) compared with that for the high-dose group (3/29 treatments) suggested no real difference in the percentage of therapeutic failures in either treatment group. The majority of therapeutic failures resulted from failure to achieve beginning of relief of symptoms by 4 hours. No relapses within 4 hours were observed in any of the groups.

Efficacy of rhC1INH to reduce the time to the beginning of relief of symptoms was found in males as well as in females (Table III). With the exception of the female 50 U/kg dose group, the 95% CIs for the hazard ratios of the subgroups were >1 , indicating that rhC1INH significantly reduced the time to the beginning of relief in these subgroups compared with the saline subgroups. The median time to the beginning of relief observed for attacks at different anatomical locations ranged from 50 to 124 minutes in the rhC1INH groups versus 243 to 560 minutes in the saline group, with hazard ratios >2 for the comparison of subgroups by anatomical location with saline (Table III). These findings indicated efficacy of rhC1INH for the treatment of angioedema attacks at all anatomical locations, although because of the small number of patients in the subgroups, the 95% CI for the hazard ratio comparing the rhC1INH subgroup with saline subgroup extended below 1. Time to beginning of the effect of treatment was independent of investigator rating of severity at baseline, and rhC1INH was effective even in attacks worsening just before treatment (Table III).

Median times to the beginning of relief of symptoms and minimal symptoms as assessed by the investigator were similar to those based on VAS scores for the rhC1INH dose groups (data in this article's Tables E11 and E12 in the Online Repository at www.jacionline.org).

TABLE I. Characteristics of eligible attacks treated

Characteristics	rhC1INH 100 U/kg (N = 29)	rhC1INH 50 U/kg (N = 12)	Saline (N = 29)
Time between onset of an attack and start time of the infusion (min)			
Median	240	347	285
Interquartile range	209-322	299-788	210-325
Range	125-1746	221-1391	140-425
Eligible locations assessed,* n (%)			
Orofacial, pharyngeal, laryngeal	4 (14)	0	10 (34)
Genitourinary	0	1 (8)	1 (3)
Peripheral	15 (52)	6 (50)	13 (45)
Abdominal	12 (41)	5 (42)	9 (31)
Course of the attack before treatment,† n (%)			
Worsening	14 (52)	6 (50)	19 (66)
Stable	5 (19)	2 (17)	4 (14)
Improving	8 (30)	4 (33)	6 (21)
VAS (mm) before start of infusion at the most serious location‡			
Mean (SD)	78.3 (15.4)	77.6 (14.4)	80.2 (14.5)
Range	28-100	51-99	49-100
Baseline complement parameters, median (range)			
Functional C1INH (% of normal)‡§	28 (28-39)	28 (28-39)	28 (28-42)
Antigenic C1INH (μg/mL)§	50 (30-365)	58 (30-87)	56 (30-360)
C1q (IU/mL)§	84 (10-143)	72 (50-92)	69 (14-115)
C4 (μg/mL)§	50 (15-215)	57 (18-100)	39 (15-208)

*Five patients (2 of the 100 U/kg group and 3 of the saline group) had multiple eligible locations.

†See this article's Table E7 in the Online Repository at www.jacionline.org for definitions.

‡Lower limit of detection, 28%.

§Normal values: functional C1INH, 70% to 130% of normal; antigenic C1INH, 210-390 μg/mL; C1q, 34-96 IU/mL; C4, 100-400 μg/mL.

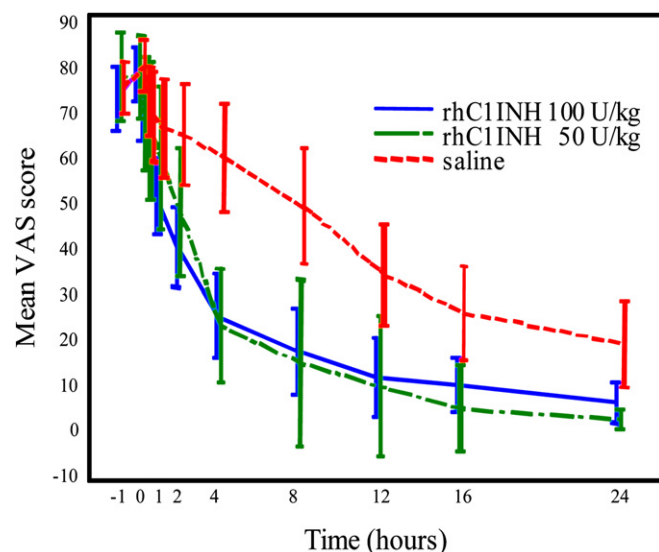


FIG 2. Course of mean VAS scores in time in the rhC1INH and saline groups. Data indicate mean VAS scores and 95% CIs.

Safety of rhC1INH

No patient was discontinued because of an adverse reaction. TEAEs occurred less frequently in the rhC1INH groups (27 TEAEs in 7 patients treated with 100 U/kg and 6 TEAEs in 4 patients of the 50 U/kg group; see this article's Tables E13 and E14 in the Online Repository at www.jacionline.org) than in the saline group (33 TEAEs in 14 patients). One TEAE possibly or probably related to study medication administration occurred in

the rhC1INH 100 U/kg dose group compared with 3 in the saline group. Events that were assessed as related to study treatment in patients exposed to rhC1INH were headache and vertigo; events that were assessed as related to study treatment in the patients receiving placebo were headache, injection site swelling, epistaxis, and hypotension. One serious AE (colitis 31 days after treatment) occurred in the rhC1INH 100 U/kg dose group, no serious AE in the 50 U/kg group, and 3 in the saline group. None of these serious AEs were considered by the investigator to be possibly, probably, or definitely related to study drug. There were no clinically relevant changes in hematology, routine chemistry or urinalysis results, electrocardiogram, and vital signs parameters.

Postexposure levels of antirabbit milk protein antibodies were below the cutoff level of the assay for all patients treated with rhC1INH except for 1 patient treated with 50 U/kg rhC1INH, who had antibodies on 1 occasion just above the cutoff level value, but tested negative in a confirmatory displacement assay.

No change in anti-C1INH antibodies pre-exposure and post-exposure was detected. Pre-exposure to rhC1INH, 2 patients had IgG antibodies against C1INH just above the cutoff level of the assay. Postexposure samples were negative in all patients except for 2 who showed just above cutoff values on a single occasion. All samples with above cutoff values of IgG against C1INH tested negative in an assay for neutralizing antibodies (results not shown). Results for IgM or IgA anti-C1INH antibodies determinations were all negative, both pre-exposure and postexposure.

DISCUSSION

Recombinant human C1INH was developed to offer an alternative to plasma-derived C1INH for the treatment of acute

TABLE II. Primary and secondary efficacy outcome in the 3 treatment groups

Efficacy outcomes	rhC1INH 100 U/kg (N = 29)	rhC1INH 50 U/kg (N = 12)	Saline (N = 29)
Time to beginning of relief of symptoms (min)			
Median (95% CI)	66 (61-122)	122 (72-136)	495 (245-520)
Hazard ratio (95% CI) against saline	3.26 (1.85-5.74)	2.68 (1.23-5.85)	NA
Cox PH <i>P</i> value	<.001	.013	NA
Time to minimal symptoms (min)			
Median (95% CI)	266 (242-490)	247 (243-484)	1210 (970-1500)
Hazard ratio (95% CI) against saline	2.62 (1.48-4.61)	3.86 (1.71-8.72)	NA
Cox PH <i>P</i> value	<.001	.001	NA

NA, Not applicable.

The hazard ratios and Cox PH *P* value were calculated from a Cox PH model with treatment and study included as factors.

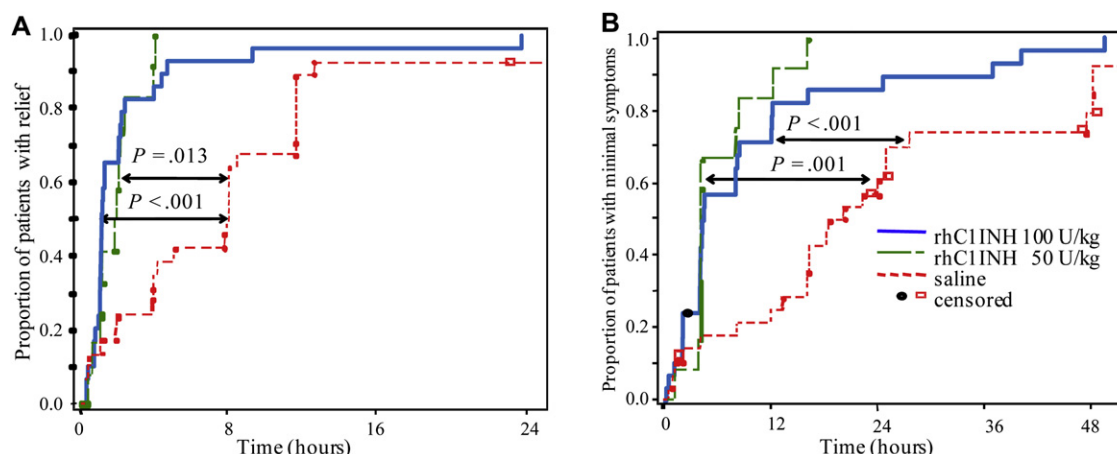


FIG 3. Kaplan-Meier plot of time (minutes) from start of infusion to the beginning of relief of symptoms (A) or of minimal symptoms (B). Patients, who did not have beginning of relief of symptoms or minimal symptoms during the observation period, were censored at the time the last overall VAS score was recorded (indicated with a tag). One patient of the saline group with censored onset of relief >2000 minutes is not indicated in the graph. Modified with permission from Frank MM, Recombinant and plasma-purified human C1 inhibitor for the treatment of hereditary angioedema, p S31. In: New perspectives in hereditary angioedema (HAE): molecular mechanisms & therapeutic choices. *World Allergy Organization Journal* 2010 Supplement;3(9):s29-40.

angioedema attacks in patients with HAE. Two randomized, placebo-controlled studies, 1 in Europe and 1 in North America, were undertaken to evaluate the efficacy of rhC1INH as a treatment for acute angioedema attacks in patients with HAE. Both studies had similar protocols, and both studies included fewer patients than foreseen because they both were stopped when a predefined interim analysis revealed they had met their primary and secondary endpoint. The analysis of the pooled data of both studies is therefore presented here.

No clinical test can objectively assess the severity of an HAE attack because of the variability of symptoms and of anatomical locations. Therefore, a new patient-reported outcome instrument was designed and validated in accordance with regulatory guidance.²⁴⁻²⁶ An interview study with 17 patients with HAE demonstrated that the HAE-specific VAS instrument was suitable for assessment and estimation of degree and duration of acute angioedema symptoms (J. Speight, unpublished data, 2009). Subsequently, a quantitative psychometric validation was performed to evaluate the measurement properties of the VAS instrument, which demonstrated the test-retest reliability and convergent validity of the overall severity VAS compared with patient symptoms and investigator symptom scoring (L. Kaufman, unpublished data, 2009). In addition, these studies supported the

clinical significance of the minimal difference used to define the primary endpoint—that is, 20 mm.

The North American study evaluated 100 and 50 U/kg of rhC1INH as a treatment for acute angioedema attacks in HAE. The seemingly different median times to the beginning of relief of symptoms of either dose presumably reflects an artifact of the protocol caused by the discrete time points of data collection rather than a real difference in efficacy of these doses. Notably, the 95% CIs of the median time to the beginning of relief of either group are overlapping (Table II), and the Kaplan-Meier plots of both dose groups show no difference in response (Fig 3). Second, all patients receiving the 50 U/kg dose responded to treatment within 4 hours, and no therapeutic failures were observed in this dose group. In addition, an open-label extension study evaluated 168 administrations in 62 patients. The median time to the beginning of relief was approximately 1 hour. These data further support the safety and efficacy of the 50U/kg dose, irrespective of anatomical location, including laryngeal attacks (data not shown).

Three of the 41 (7%) patients receiving rhC1INH had a therapeutic failure, 1 because of use of medication that may have interfered with the assessment of efficacy and 2 because of lack of the beginning of relief of symptoms within 4 hours, yielding a response rate of 93% of the patients within 4 hours on rhC1INH

TABLE III. Subgroup analysis of time to beginning of relief of symptoms using Cox PH modeling

Subgroup	rhC1INH (100 U/kg) (N = 29)	rhC1INH (50 U/kg) (N = 12)	Saline (N = 29)
Male patients			
Median (95% CI)*	64.0 (40.0-128.0)	74.5 (46.0-250.0)	496.0 (480.0-720.0)
Hazard ratio (95% CI)†	37.24 (4.15-334.58)	38.47 (2.93-504.83)	
N	13	4	8
Female patients			
Median (95% CI)	67.0 (62.0-123.0)	125.5 (72.0-148.0)	320.0 (125.0-718.0)
Hazard ratio (95% CI)	2.53 (1.25-5.12)	2.06 (0.83-5.09)	
N	16	8	21
Abdominal attacks			
Median (95% CI)	50 (40-68)	70 (29-148)	243 (35-720)
Hazard ratio* (95% CI)	2.52 (0.92-6.87)	2.99 (0.76-11.80)	
N	12	5	9
Peripheral attacks			
Median (95% CI)	75 (63-128)	124 (79-136)	560 (480-720)
Hazard ratio (95% CI)	3.93 (1.68-9.16)	3.15 (0.97-10.23)	
N	15	6	13
Oro-facial-pharyngeal-laryngeal attacks			
Median (95% CI)	70.0 (60.0-120.0)		306.0 (70.0-495.0)
Hazard ratio (95% CI)			
N	4		10
Worsening attacks‡			
Median (95% CI)	64.5 (55.0-75.0)	128.0 (70.0-148.0)	487.0 (120.0-496.0)
Hazard ratio (95% CI)	3.55 (1.64-7.67)	2.79 (0.98-7.94)	
N	16	7	19
Mild or moderate attacks§			
Median (95% CI)	65.0 (61.0-128.0)	121.0 (72.0-128.0)	289.0 (120.0-718.0)
Hazard ratio (95% CI)	2.96 (1.19-7.38)	1.97 (0.70-5.52)	
N	10	7	14
Severe attacks§			
Median (95% CI)	68.0 (60.0-123.0)	136.0 (29.0-250.0)	495.0 (243.0-720.0)
Hazard ratio (95% CI)	5.08 (2.15-12.03)	4.79 (1.37-16.76)	
N	19	5	15

*Median time to the beginning of relief in minutes (95% CI).

†Hazard ratios comparing against saline.

‡Worsening defined as overall severity VAS score at the start of infusion (timepoint = 0 h) greater than the score at time of evaluation (timepoint = -1 h).

§Mild, moderate, severe defined by investigator's score (2, 3, and 4, respectively).

administration. This response rate is similar to that reported by Waytes et al¹⁴ with plasma-derived C1INH at 25 U/kg, although in the extension phase of the same study, a lower response rate was observed.¹⁵ In the largest published placebo-controlled study with plasma-derived C1INH, only abdominal and facial angioedema locations were included, and patient-reported improvement of symptoms was used to assess efficacy.¹³ Although these differences in study design make direct comparison of study results difficult, the latter study shows that efficacy of replacement therapy with C1INH in acute angioedema attacks is dose-dependent. Doses of 10 U/kg, which have been generally recommended in clinical practice,²⁷⁻³¹ offered no significant benefit over placebo, and a statistically significant effect was only observed at a dose of 20 U/kg. Thus, the higher response rate to rhC1INH may reflect the higher doses (50 and 100 U/kg) used compared with studies with plasma-derived C1INH.

The main pharmacologic difference between plasma-derived and recombinant C1INH is the shorter half-life of the latter (approximately 3 hours vs >20 hours for plasma-derived C1INH).^{17,31} The duration of an untreated angioedema attack can be several days. Therefore, the possibility that a single infusion of rhC1INH cannot completely cure an attack should be considered. However, none of the patients treated with rhC1INH had

a relapse of the angioedema attack. Thus, the shorter half-life of rhC1INH compared with that of the plasma-derived products has no significant impact on the treatment of acute attacks. Thus, dose seems to be more important for efficacy of C1INH in angioedema attacks than half-life.

Experience with plasma-derived C1INH has shown that administration of this inhibitor is safe and well tolerated.^{12,13,15,29,32,33} Accordingly, the frequency of AEs was low in the rhC1INH groups. In addition, except for a few isolated occasional increases just above the cutoff level of the assays, postexposure plasma samples were negative for antibodies against C1INH or rabbit milk proteins. This safety profile of rhC1INH is supported by accumulating experience with ongoing open-label studies (data not shown). The only hypersensitivity reaction observed with over 500 administrations of rhC1INH occurred in a healthy volunteer who had failed to disclose a history of rabbit allergy and who appeared to have high levels of pre-existing IgE against rabbit epithelium (dander).³⁴ RhC1INH is therefore contraindicated in patients with a history of rabbit allergy.

In conclusion, rhC1INH constitutes a highly effective alternative to plasma-derived C1INH for the treatment of acute angioedema attacks in patients with HAE.

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Clinical implications: rhC1INH at 100 or 50 U/kg represents a new, highly effective alternative to plasma-derived C1INH for acute replacement therapy in the treatment of angioedema attacks in patients with HAE.

REFERENCES

- Bygum A. Hereditary angio-edema in Denmark: a nationwide survey. *Br J Dermatol* 2009;161:1153-8.
- Zuraw BJ. Hereditary angioedema. *N Engl J Med* 2008;359:1027-36.
- Pappalardo E, Caccia S, Suffritti C, Tordai A, Zingale LC, Cicardi M. Mutation screening of C1 inhibitor gene in 108 unrelated families with hereditary angioedema: functional and structural correlates. *Mol Immunol* 2008;45:3536-44.
- Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001;161:2417-29.
- Rosen FS, Alper CA, Pensky J, Klempner MR, Donaldson VH. Genetically determined heterogeneity of the C1 esterase inhibitor in patients with hereditary angioneurotic edema. *J Clin Invest* 1971;50:2143-9.
- Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 Esterase Inhibitor Deficiency Workshop and beyond. *J Allergy Clin Immunol* 2004;114:S51-131.
- Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206-15.
- Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976;84:580-93.
- Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc* 2000;75:349-54.
- Nussberger J, Cugno M, Cicardi M. Bradykinin-mediated angioedema. *N Engl J Med* 2002;347:621-2.
- Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE III. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 2002;109:1057-63.
- Prematta MJ, Prematta T, Craig TJ. Treatment of hereditary angioedema with plasma-derived C1 inhibitor. *Therapeutics and clinical risk management* 2008;4:975-82.
- Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009;124:801-8.
- Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med* 1996;334:1630-4.
- Kunschak M, Engl W, Maritsch F, Rosen FS, Eder G, Zerlauth G, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion* 1998;38:540-9.
- Nuijens JH, Hack CE. Recombinant C1 inhibitor. *J Allergy Clin Immunol* 2004;114:S100-4.
- Van Doorn MBA, Burggraaf J, van Dam T, Eerenberg A, Levi M, Hack CE, et al. A phase I study of recombinant human C1 inhibitor in asymptomatic patients with hereditary angioedema. *J Allergy Clin Immunol* 2005;116:876-83.
- Choi G, Soeters MR, Farkas H, Varga L, Obtulowicz K, Bilo B, et al. Recombinant human C1-inhibitor in the treatment of acute angioedema attack. *Transfusion* 2007;47:1028-32.
- Nuijens JH, Verdonk R, Resink T, Visscher S, van Doorn M, Choi G, et al. Open-label studies of recombinant human C1 Inhibitor (rhC1INH) in patients with acute attacks of hereditary angioedema [abstract]. Available at: <http://www.haenet.hu/new/abstractbook.pdf>. Accessed August 31, 2010.
- Wagenaar-Bos IG, Drouet C, Aygören-Pürsün E, Bork K, Bucher C, Bygum A, et al. Functional C1-inhibitor diagnostics in hereditary angioedema: assay evaluation and recommendations. *J Immunol Meth* 2008;338:14-20.
- Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (icatibant). *J Allergy Clin Immunol* 2007;119:1497-503.
- Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Emerg Med* 1996;27:485-9.
- Gallagher EJ, Bijur PE, Latimer C, Silver W. Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *Am J Emerg Med* 2002;20:287-90.
- European Medicines Agency. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. Available at: <http://www.ispor.org/workpaper/EMEA-HRQL-Guidance.pdf>. Accessed July 27, 2005.
- Food and Drug Administration. Guidance for industry: patient-reported outcomes: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.
- Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research; 2009. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>. Accessed December 2009.
- Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 2001;161:714-8.
- Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. *Allergy* 2008;63:751-7.
- Bork K, Meng G, Staubach P, Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 2005;45:1774-84.
- Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, Zingale L, et al. Canadian 2003 International Consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004;114:629-37.
- Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, von Hentig N, Klingebiel T, Kreuz W. Pharmacokinetic analysis of human plasma-derived pasteurized C1-inhibitor concentrate in adults and children with hereditary angioedema: a prospective study. *Transfusion* 2010;50:354-60.
- Cicardi M, Zingale LC, Zanichelli A, Delilieri DL, Caccia S. The use of plasma-derived C1 inhibitor in the treatment of hereditary angioedema. *Expert Opin Pharmacother* 2007;8:3173-81.
- Zuraw B, Busse P, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;363:513-22.
- Nuijens J, Verdonk R, Giannetti B, Visscher S, van Doorn M, Resink T, et al. Clinical studies of recombinant human C1 inhibitor (rhC1INH) in patients with acute attacks of hereditary angioedema [abstract]. *J Allergy Clin Immunol* 2008;115 (suppl):S202.

TABLE E1. Inclusion and exclusion criteria of patients with HAE at screening

For inclusion in the studies, patients had to fulfill all of the following criteria at screening:

- Age 12 y and above (North American study) or 16 y and above (European study).
- Signed written informed consent (and written assent, for minors).
- Clinical and (central) laboratory diagnosis of HAE with baseline plasma level of functional C1INH <50% of normal (and in the North American study without evidence for acquired angioedema (AAE) by a low plasma level of C1q and/or presence of anti-C1INH antibodies).
- If female, a negative pregnancy test, intent to avoid pregnancy for the duration of the study, used an accepted, effective method of contraception if child-bearing was possible. This criterion was used only in the North American study.

Patients who met any of the following exclusion criteria were not included in the study:

- A history of administration of pharmaceuticals derived from rabbits (eg, antisera, rhC1INH) in conjunction with any evidence of an allergic reaction.
- A history of anaphylaxis, or severe allergies (ie, requiring medication) to food, proteins, and/or drugs.
- A history of allergic reactions to C1INH concentrates or any rabbit protein.
- A diagnosis of acquired C1INH deficiency (excluded patients with AAE).
- Pregnancy, breast-feeding, or current intention to become pregnant.
- Known or suspected addiction to narcotics.
- Blood donation in the past 3 mo (90 d).
- Treatment with another investigational drug in another clinical study in the past month (≤ 30 d in the North American study, <3 mo in the European study).
- Any clinically significant abnormality in the routine hematology, biochemistry, and urinalysis tests.
- Body weight >120 kg (amended from 128 kg at Protocol Amendment 4, February 17, 2006). This criterion was only used in the North American study.
- Any condition or treatment that in the opinion of the investigator might have interfered with the evaluation of the study objectives.

TABLE E2. Inclusion and exclusion criteria of patients with HAE for randomization

For inclusion in the randomized controlled phase of the studies, the patient who presented with an acute angioedema attack to the clinical center had to fulfill all of the following criteria:

- Screening criteria (see Table E1) were still met.
- Evidence for exacerbation or development of an abdominal attack and/or of facial-orpharyngeal angioedema and/or laryngeal angioedema and/or of urogenital angioedema and/or peripheral angioedema. (In the North American study, peripheral angioedema was added as an inclusion criterion in Protocol Amendment 5, November 1, 2006).
- Onset of eligible symptoms within 5 h before medical evaluation of eligibility had occurred.
- Patient VAS score of overall severity of angioedema symptoms at least at 1 eligible location at the time of evaluation (time = -1 hours) of at least 50 mm, where 0 mm meant “no symptoms at all” and 100 mm meant “extremely disabling.”

Patients who met any of the following exclusion criteria were excluded from randomization:

- Any changes since screening that would exclude patients based on the exclusion criteria for screening.
- Patients presenting or developing a life-threatening attack (an attack requiring immediate emergency procedures to prevent death, hypoxemia-related injuries, or other unfavorable outcomes).
- Use of any disallowed concomitant medication (see Table E4) since the onset of the eligible attack

Patients were excluded from the study after randomization but before study drug administration in the following cases:

- Regression of angioedema symptoms scored with VAS score at time 0 hours; just before the administration of study medication: reduction of 20 mm or more (beginning of relief) in VAS score (at time 0 hours) for overall severity of symptoms of angioedema at eligible location compared with VAS score at time 1 hours.
- Strong evidence that symptoms were not related to HAE.

In the case of strong evidence that symptoms were not related to HAE or in case of regression of angioedema signs after randomization, but just before planned study medication administration (time 0 hours), study medication was not administered. Such patients who had not received study medication were not considered in the intention-to-treat analyses.

TABLE E3. Efficacy study schedule

Procedures	Screen	Occasion													
Time		−1 h	−45′	0′	15′	30′	1 h	2 h	4 h	8 h	12 h	16 h	24 h	48 h	72 h
Hospitalization		X	X	X	X	X	X	X	X	*	*	*	*		
Study drug infusion				X											
Demographics	X														
Medical history	X														
Assessment of angioedema signs (VAS)		X		X	X	X	X	X	X	*	*	X	X	X	X
Investigator score		X		X	X	X	X	X	X	*	*	*	X	X	X

*Only if the patient was still hospitalized (in the European study, 8-h and 12-h assessments were initially performed in all patients treated. As a consequence, all patients had to stay in the hospital, irrespective of whether they had recovered from the attack. Later in the study, an amendment was implemented that allowed patients with minimal or no symptoms to be discharged from the hospital).

TABLE E4. Definition of therapeutic failure

Therapeutic failure in case any of the following occurs:
● The beginning of relief of symptoms more than 4 h after baseline ● Relapse of the attack (defined as an increase of VAS score to baseline value or higher after beginning of relief had occurred within the first 4 h) ● A new location of the attack (overall VAS score greater than 0 at any time up to 4 h for a location that had an overall VAS score of 0 (or missing VAS score) at baseline) ● Use of medication that may interfere with the assessment of the impact of rhC1INH on efficacy measures before time of the beginning of relief: - Narcotics identified by ATC codes starting with N02A - C1INH identified by ATC codes starting with B02AB - Fresh frozen plasma identified by ATC codes starting with B05AA - Analgesics identified by ATC codes starting with N02 - Antiemetics identified by ATC codes starting with A04A - Tranexamic acid identified by ATC codes starting with B02AA* - Epsilonaminocaproic acid identified by ATC codes starting with B02AA*

ATC, Anatomical, Therapeutic, Chemical.
*Only resulting in therapeutic failure when the dose was increased from the onset of the attack.

TABLE E5. Demographics of treated and not treated eligible patients on screening

Demographic parameters	North American study		European study	
	Treated	Not treated	Treated	Not treated
Patients (n)	38	93	32	127
Sex (F/M)	28/10	59/34	17/15	75/52
Age (y), mean $\pm$ SD	35.3 $\pm$ 13.3	40.2 $\pm$ 13.3	44.5 $\pm$ 15.4	40.8 $\pm$ 13.5
Weight (kg), mean $\pm$ SD	77.3 $\pm$ 19.3	82.8 $\pm$ 20.4	80.2 $\pm$ 18.9	70.5 $\pm$ 15.2
Severe attacks/y, mean $\pm$ SD	16 $\pm$ 13	15 $\pm$ 28	18 $\pm$ 44	8 $\pm$ 18
Prophylactic medication* (yes/no)	32/6	69/24	21/11	74/53

F, Female; M, male.

*Antifibrinolytics, androgens, plasma-derived C1INH, or combinations thereof.

TABLE E6. Demographic data of the patients with HAE who received randomized treatment

Demographic parameters	rhC1INH (100 U/kg)		rhC1INH (50 U/kg)	Saline	
	North American (N = 13)	European (N = 16)	North American (N = 12)	North American (N = 13)	European (N = 16)
Age on date of attack (y)					
Mean	34.2	46.1	40.7	32.4	44.5
SD	15.7	14.5	12.2	11.3	16.8
Range	17-66	19-67	20-59	17-55	17-71
Categorized age, n (%)					
<18 y	1 (8)	0	0	1 (8)	1 (6)
18-65 y	11 (85)	14 (88)	12 (100)	12 (92)	12 (75)
≥65 y	1 (8)	2 (13)	0	0	3 (19)
Sex, n (%)					
Male	5 (38)	8 (50)	4 (33)	1 (8)	7 (44)
Female	8 (62)	8 (50)	8 (67)	12 (92)	9 (56)
Race, n (%)					
White	12 (92)	16 (100)	12 (100)	11 (85)	16 (100)
Black	0	0	0	1 (8)	0
Asian	1 (8)	0	0	1 (8)	0
Height (cm)					
Mean	168.8	171.2	170.2	164.8	170.6
SD	7.2	11.3	8.1	6.8	9.7
BMI on admission (kg/m ²)					
Mean	26.1	28.9	29.8	25.6	26.2
SD	5.3	6.4	7.1	5.8	4.8
Body weight on admission (kg)					
Mean	75.1	84.2	86.6	69.9	77.3
SD	19.2	18.0	22.7	15.7	20.4

BMI, Body mass index.

TABLE E7. Explanations of terms used in Table I

Term	Definition
Worsening attack	Angioedema attack with VAS increasing between start infusion (T = 0) and evaluation (T = -1 h)
Stable attack	Angioedema attack with VAS staying the same between start infusion (T = 0) and evaluation (T = -1 h)
Improving attack	Angioedema attack with VAS decreasing between start infusion (T = 0) and evaluation (T = -1 h)
Order of clinical seriousness of attack	Attack with laryngeal location; attack with abdominal location; attack with orofacial-pharyngeal location; attack with genitourinary location; attack with peripheral location

T, Timepoint.

TABLE E8. Patient disposition

Patient disposition	rhC1INH 100 U/kg (N = 29)	rhC1INH 50 U/kg (N = 12)	Saline (N = 29)
North American study, n (%)	13 (45)	12 (100)	13 (45)
European study, n (%)	16 (55)	NA	16 (55)
Patients who completed assessments up to day 90, n (%)	27 (93)	10 (83)	25 (86)
Patients who discontinued to enter the open label extension phase, n (%)	1 (3)	1 (8)	2 (7)
Patients who prematurely discontinued, n (%)	1 (3)	1 (8)	2 (7)
North American study, n	0	1	1
European study, n	1	NA	1

NA, Not applicable.

TABLE E9. Comparison of median time to the beginning of relief of symptoms and median time to minimal symptoms in the European and North American studies

Outcome	rhC1INH (100 U/kg) median (95% CI)	Saline median (95% CI)
Time to beginning of relief (min)		
European study	64 (40-123)	520 (480-720)
North American study	68 (62-132)	258 (240-495)
Combined	66 (61-122)	495 (245-520)
Time to minimal symptoms (min)		
European study	480 (243-723)	1440 (720-2885)
North American study	245 (125-270)	1101 (970-1494)
Combined	266 (242-490)	1210 (970-1500)

TABLE E10. Number of patients with therapeutic failure

Therapeutic failure	rhC1INH (100 U/kg) (N = 29)	rhC1INH (50 U/kg) (N = 12)	Saline (N = 29)
Therapeutic failure, n (%)	3 (10)	0	17 (59)
No therapeutic failure, n (%)	26 (90)	12 (100)	12 (41)
Odds ratio for dose group vs saline (95% CI)	0.06 (0.01-0.32)	0.13 (0.00-1.08)	
<i>P</i> value*	<.001	.060	

*Calculated from an exact logistic regression including terms for study and dose group.

TABLE E11. Time to the beginning of relief of symptoms by investigator’s score

Primary endpoint	rhC1INH (100 U/kg) (N = 29)	rhC1INH (50 U/kg) (N = 12)	Saline (N = 29)
Median (95% CI)	54 (30-64)	71 (42-124)	245 (60-495)
Hazard ratio (95% CI) against saline	2.47 (1.42-4.32)	1.61 (0.76-3.43)	NA
Cox PH <i>P</i> value	.001	.214	NA

NA, Not applicable.
Investigator’s score (IS): Investigators assessed the severity of angioedema symptoms at the same time points for each location by using a 6-point IS ranging from 0 (no symptoms) to 5 (life-threatening symptoms). Beginning of relief by IS: a decrease of ≥ 1 by IS compared with baseline at any eligible location. Minimal symptoms by IS: IS ≤ 1 for all locations of the attack.

TABLE E12. Time to minimal symptoms by investigator's score

Time to minimal symptoms by investigator's score			
Secondary endpoint	rhC1INH (100 U/kg) (N = 29)	rhC1INH (50 U/kg) (N = 12)	Saline solution (N = 29)
Median (95% CI)	268 (244-745)	250 (242-265)	780 (255-1440)
Hazard ratio (95% CI) against saline	1.68 (0.95-2.96)	1.95 (0.90-4.22)	NA
Cox PH <i>P</i> value	.072	.089	NA

NA, Not applicable.

Investigator's score (IS): Investigators assessed the severity of angioedema symptoms at the same time points for each location by using a 6-point IS ranging from 0 (no symptoms) to 5 (life-threatening symptoms). Beginning of relief by IS: a decrease of ≥ 1 by IS compared with baseline at any eligible location. Minimal symptoms by IS: IS ≤ 1 for all locations of the attack.

TABLE E13. Overview of TEAEs in the study population

TEAEs	rhC1INH (100 U/kg) (N = 29)	rhC1INH (50 U/kg) (N = 12)	Saline (N = 29)
Total no. of TEAEs	27	6	33
Patients with at least the following:			
1 TEAE, n (%)	7 (24)	4 (33)	14 (48)
1 Treatment-related TEAE, n (%)	1 (3)	0	3 (10)
1 Severe TEAE, n (%)	1 (3)	2 (17)	6 (21)
1 Serious TEAE, n (%)	1 (3)	0	3 (10)
1 TEAE leading to permanent discontinuation	0	0	0

TEAE, AE occurring during observation period (90 days) with onset of study drug administration. Treatment-related TEAE: TEAE assessed by investigator as possibly, probably, or definitely related to study treatment.

TABLE E14. Overview of TEAEs observed during 90 days follow-up of the study population

System Organ Class and AE preferred term (Medical Dictionary for Regulatory Activities v9.1)	rhC1INH 100 U/kg (N = 29)	rhC1INH 50 U/kg (N = 12)	Saline (N = 29)
	n (%)	n (%)	n (%)
Gastrointestinal disorders	3 (10)	0	4 (14)
Abdominal pain	1 (3)	0	2 (7)
Abdominal pain upper	0	0	1 (6)
Colitis	1 (3)	0	0
Diarrhea	1 (3)	0	0
Vomiting	0	0	0
Nervous system disorders	3 (10)	0	4 (14)
Headache	3 (10)	0	4 (14)
Vertigo	1 (3)	0	0
Infections and infestations	2 (7)	2 (17)	1 (3)
Cystitis	0	0	1 (3)
Fungal infection	0	0	1 (3)
Herpes simplex	1 (3)	0	0
Sinusitis	1 (3)	0	0
Tonsillitis	1 (3)	0	0
Tooth abscess	0	1 (8)	0
Urinary tract infection	0	1 (8)	0
General disorders and administration site conditions	1 (3)	1 (6)	2 (13)
Pain	0	0	2 (7)
Condition aggravated	1 (3)	0	0
Injection site swelling	0	0	1 (3)
Mucosal hyperemia	0	0	1 (3)
Pyrexia	0	0	1 (3)
Investigations	1 (3)	1 (8)	1 (3)
C-reactive protein	0	1 (8)	0
Hematocrit increased	1 (3)	0	0
Hemoglobin increased	1 (3)	0	0
Prostate examination	0	0	1 (6)
Skin and subcutaneous tissue disorders	0	2 (17)	1 (3)
Erythema	0	1 (8)	0
Pruritus	0	1 (8)	0
Rash erythematous	0	0	1 (3)
Musculoskeletal and connective tissue disorders	0	1 (8)	2 (7)
Back pain	0	1 (8)	0
Myalgia	0	0	0
Pain in extremity	0	0	1 (3)
Respiratory, thoracic, and mediastinal disorders	1 (3)	0	2 (7)
Epistaxis	0	0	1 (3)
Nasal congestion	1 (3)	0	0
Pharyngeal inflammation	1 (3)	0	0
Throat irritation	0	0	1 (3)
Reproductive system and breast disorders	2 (7)	0	0
Menstrual disorder	1 (3)	0	0
Scrotal swelling	1 (3)	0	0
Renal and urinary disorders	1 (3)	0	1 (3)
Calculus ureteric	0	0	1 (3)
Renal failure acute	1 (3)	0	0
Congenital, familial, and genetic disorders	0	0	1 (3)
HAE*	0	0	1 (3)
Hepatobiliary disorders	0	0	1 (3)
Biliary colic	0	0	1 (3)
Psychiatric disorders	0	0	1 (3)
Insomnia	0	0	1 (3)
Surgical and medical procedures	0	0	1 (3)
Ureteric calculus removal	0	0	1 (3)
Vascular disorders	0	0	1 (3)
Hypotension	0	0	1 (3)

*One patient reported HAE as a new attack at new location.