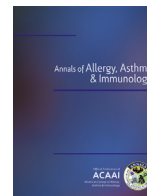




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Recombinant human C1 esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial

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ABSTRACT

Background: Hereditary angioedema (HAE), caused by C1 inhibitor (C1INH) deficiency or dysfunction, is characterized by recurrent attacks of tissue swelling affecting multiple anatomic locations. Recombinant human C1INH (rhC1INH) has been shown effective for acute treatment of HAE attacks.

Objective: To evaluate the efficacy and safety of rhC1INH (50 IU/kg to maximum 4,200 IU/treatment) vs placebo in a larger HAE population.

Methods: Seventy-five patients experiencing peripheral, abdominal, facial, and/or oropharyngeal laryngeal attacks were randomized (3:2) to rhC1INH (n = 44) or placebo (saline; n = 31). Efficacy was assessed by patient responses on a Treatment Effect Questionnaire (TEQ) and visual analog scale (VAS). Safety also was evaluated.

Results: Median (95% confidence interval) time to beginning of symptom relief at the primary attack location was 90 minutes (61–150) in rhC1INH-treated patients vs 152 minutes (93, not estimable) in placebo-treated patients (P = .031) based on the TEQ and 75 minutes (60–105) vs 303 minutes (81–720, P = .003) based on a VAS decrease of at least 20 mm. Median time to minimal symptoms was 303 minutes (240–720) in rhC1INH-treated patients vs 483 minutes (300–1,440) in placebo-treated patients based on the TEQ (P = .078) and 240 minutes (177–270) vs 362 minutes (240, not estimable; P = .005), based on an overall VAS less than 20 mm. Overall, rhC1INH was safe and well tolerated; no thromboembolic events, anaphylaxis, or neutralizing antibodies were observed.

Study registered at <http://www.clinicaltrials.gov>; identifier NCT01188564.

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Conclusion: Relief of symptoms of HAE attacks was achieved faster with rhC1INH compared with placebo as assessed by the TEQ and VAS, with a positive safety profile. Results are consistent with previous studies showing efficacy and safety of rhC1INH in patients with HAE.

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Introduction

Hereditary angioedema (HAE) caused by a deficiency of endogenous C1 inhibitor (C1INH) is a rare, serious, autosomal-dominant genetic disorder with an estimated prevalence of 1 in 50,000.¹ Patients with HAE owing to C1INH deficiency experience episodic, recurrent attacks of soft tissue swelling affecting multiple anatomic regions, including the gastrointestinal tract, face, larynx, oropharynx, urogenital areas, and extremities. These edematous attacks are associated with considerable morbidity, often requiring hospitalization and immediate medical intervention. Laryngeal attacks may be life threatening owing to the risk of asphyxiation.

C1 inhibitor therapy with human plasma-derived C1INH (pdC1INH) products has been approved for prophylaxis and acute treatment of HAE attacks. However, pdC1INH products have a potential risk of transmission of human blood-borne pathogens. In addition, thrombotic events have been reported in association with the use of pdC1INH products.^{2–4} Because production of plasma-derived products depends on the availability of donor plasma, shortages of plasma products, including pdC1INH, have occurred.^{5,6}

Recombinant human C1INH (rhC1INH) is a novel, highly purified human C1INH extracted from the milk of transgenic rabbits.⁷ It was developed to offer a safe and effective alternative to pdC1INH products for acute treatment of HAE attacks. In controlled clinical studies, treatment with rhC1INH was shown to be safe, with no risk of transmission of human blood-borne pathogens, and no thrombotic events were reported across 190 subjects treated with 714 administrations of rhC1INH.^{8–12} In addition to the advantages presented by transgenic animals, including the ability to produce active proteins exhibiting complex post-translational modifications (eg, glycosylation, cleavage, folding), the transgenic rabbit platform ensures a reliable and scalable supply of product of uniform quality that is not dependent on human plasma donors.^{7,13}

The efficacy and safety of rhC1INH in the treatment of HAE symptoms were evaluated in 2 independent, randomized, placebo-controlled, double-blinded studies and 2 open-label extension studies. In the randomized controlled trials, patients treated with rhC1INH 50 IU/kg (12 patients) or 100 IU/kg (29 patients) had significantly shorter times to beginning of relief from symptoms and to minimal symptoms, assessed using visual analog scales (VASs), compared with placebo-treated patients.⁸ The efficacy of rhC1INH was maintained during treatment of subsequent attacks in the extension studies.^{9,10} No patients developed neutralizing antibodies to rhC1INH after repeated treatments, and single and repeated doses of rhC1INH were generally safe and well tolerated.

The normal range of C1INH activity in the plasma is 0.7 to 1.3 IU/mL (70% to 130% activity), whereas the average plasma level of C1INH activity in patients with HAE is approximately 0.2 IU/mL (20% of normal).¹⁴ Population pharmacokinetic analyses have demonstrated that rhC1INH dosing at 50 IU/kg (up to maximum of 4,200 IU/treatment) achieves C1INH activity of 0.7 in more than 90% of patients.¹¹ In an indirect comparison of reported response rates within 4 hours (corrected for response in the corresponding placebo group) with different doses of pdC1INH (10 to 25 IU/kg) or rhC1INH (50 IU/kg) in the acute treatment of attacks of HAE, the higher rhC1INH dosing regimen appeared to provide improved efficacy.¹⁵

The present randomized controlled study was conducted to extend previous studies and evaluate the efficacy and safety of rhC1INH (50 IU/kg up to a maximum of 4,200 IU/treatment)

compared with placebo for the treatment of acute angioedema attacks in a larger cohort of patients with HAE.

Methods

This was a randomized, double-blinded, placebo (saline)-controlled, multicenter, multinational study with an open-label extension phase. The results of the randomized controlled phase of the study are described in this report; results of the open-label extension phase will be reported separately. The study was conducted in compliance with the Declaration of Helsinki and national regulatory provisions. The ethics committee or the institutional review board at each study center approved the study protocol before patient enrollment. Written informed consent was obtained from all study participants before enrollment.

Seventy-five patients at least 13 years old (≥ 18 years old for patients outside the United States and Canada) with a clinically suspected and laboratory-confirmed diagnosis of HAE (baseline plasma C1INH activity $< 50\%$ of normal and no evidence of acquired angioedema) were randomized centrally (3:2) to receive a double-blinded intravenous injection of rhC1INH (50 IU/kg for patients weighing < 84 kg or 4,200 IU for patients weighing ≥ 84 kg; $n = 44$) or placebo ($n = 31$) for treatment of an eligible angioedema attack. Randomization was stratified by sex and by primary attack location (see below).

Patients were eligible for treatment if (1) the location of the attack was peripheral (extremities), abdominal, facial, and/or oropharyngeal-laryngeal; (2) the onset of these attacks occurred within 5 hours before presentation to the clinic; (3) their Overall Severity VAS score was at least 50 mm at presentation and just before dosing; and (4) there was no evidence of regression of symptoms (ie, no decrease ≥ 20 mm in Overall Severity VAS score) between presentation and dosing. Patients with life-threatening symptoms at presentation were excluded from randomization and treated with the appropriate standard of care. Four hours after dosing, rescue medication (open-label rhC1INH 50 IU/kg up to a maximum of 4,200 IU) could be provided to patients who did not achieve the beginning of relief from symptoms and had a significant degree of pain, discomfort, or disability from their HAE symptoms. At any time, at the discretion of the investigator(s), patients were allowed to receive any other rescue HAE medication for HAE attacks, including bradykinin receptor antagonists, kallikrein inhibitors, and plasma-derived C1INH. Rescue medication also could be provided at any time to patients who experienced life-threatening, oropharyngeal-laryngeal symptoms. If a patient received open-label rhC1INH or any other medication for the HAE attack, the time to beginning of relief from symptoms was censored at the last time that the Treatment Effect Questionnaire (TEQ) was assessed before the receipt of such medication. For patients with multiple eligible attack locations, the primary attack location was defined as the location with the highest Overall Severity VAS score at baseline.

Efficacy was assessed with the following instruments:

Treatment Effect Questionnaire

The TEQ consisted of 3 questions to assess HAE symptoms over time. At each time point for each affected anatomic location, patients assessed the severity of their symptoms (using a 7-point categorical scale, “much worse” to “much better”; question 1: to what extent has the Overall Severity of your [relevant attack

location] HAE attack changed since you received the infusion?), whether their symptoms had begun to decrease notably (“yes” or “no”; question 2: overall, has the intensity of your [relevant attack location] HAE attack symptoms begun to decrease noticeably since you received the infusion?), and whether their symptoms were minimal (barely noticeable; “yes” or “no”; question 3: at this moment, are your [relevant attack location] HAE attack symptoms minimal (barely noticeable)?). The primary efficacy end point was time to onset of sustained relief, which is recognized as a clinically relevant efficacy end point in the evaluation of HAE.^{16–18} This TEQ-based end point was defined as the time between dosing and the first time point at which the patient reported all of the following for the primary attack location:

- A response of “a little better,” “better,” or “much better” to TEQ question 1
- A response of “yes” to TEQ question 2
- Persistence of improvement at the next assessment time point (ie, the same or a better response to TEQ question 1 and a response of “yes” to TEQ question 2)

A secondary efficacy end point, time to minimal symptoms based on the TEQ, was defined as the time between dosing and the first time point at which the patient reported a response of “yes” to TEQ question 3 for all attack locations.

The TEQ was used as the primary efficacy assessment tool in this study at the request of regulatory authorities. Prior randomized controlled studies had used a 100-mm VAS, as described below.

Visual Analog Scale

The HAE-specific VAS instruments used in this study and in the 2 prior randomized controlled studies with rhC1INH⁸ provided patient assessments of the intensity of a range of symptoms pertinent to a symptomatic anatomic location or locations. After a series of location-specific priming symptom questions, the patient answered a uniform question related to the overall severity of symptoms and the patient's condition. The content validity of the symptoms assessed by the VAS and the suitability of the Overall Severity VAS score for assessing the severity of acute HAE symptoms were demonstrated in a qualitative semistructured interview study.¹⁹ A psychometric validation of the instrument indicated that the Overall Severity VAS score has robust measurement properties, and that a 20-mm change is a minimal clinically important difference. Time to onset of sustained relief from symptoms, based on the VAS, was defined as the first time point at which the Overall Severity VAS score at the primary attack location decreased by at least 20 mm compared with baseline, with persistence to the next time point. Time to minimal symptoms, based on the VAS, was defined as the time point at which the Overall Severity VAS score was lower than 20 mm at all locations at which VAS scores were recorded at baseline.

Investigator Score

The Investigator Score (IS), a 6-point ordinal scale (categories of 0 to 5), was used to assess the severity of patient symptoms at each affected anatomic location. These assessments were performed at the same times as patient evaluations of severity while patients were at the study center.

After administration of study medication, the severity of the angioedema attack was assessed by the TEQ, VAS, and the IS for each symptomatic anatomic location at 15-minute intervals for 2 hours followed by 30-minute intervals through 6 hours. After discharge at 6 hours, the patient was sent home with the TEQ and VAS forms to complete at the 8-, 12-, and 24-hour time points.

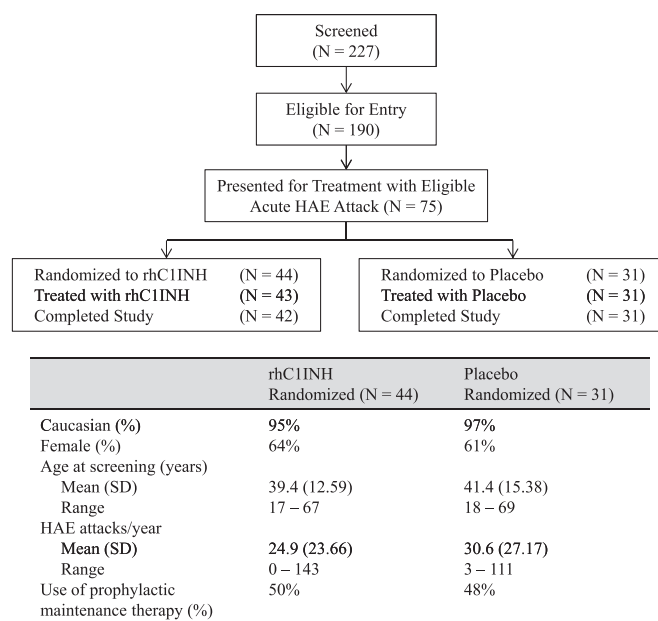


Figure 1. Patient disposition, key demographics, and hereditary angioedema (HAE) attack frequency by treatment group. The count excludes 1 patient treated with recombinant human C1 inhibitor (rhC1INH) who completed dosing but withdrew consent during the follow-up period.

Safety was monitored in all patients by direct observations, reports of adverse events and concomitant medication data, physical examinations, vital signs, electrocardiograms, clinical laboratory parameters, and immunogenicity testing. Immunogenicity tests (IgM and IgG antibodies against rhC1INH and antibodies against host-related impurities) were performed on samples obtained at screening, before treatment with study drug (rhC1INH or placebo), and at day 28 and day 90 follow-up visits.

Patients who did not achieve the beginning of persistent relief from symptoms during the 24-hour assessment period were censored at their last assessment time point (ie, they were excluded from the efficacy analysis from that point forward). Patients who received a disallowed concomitant medication or open-label rhC1INH as rescue medication before achieving the beginning of persistent relief from symptoms were censored at the last time that the TEQ was assessed before receipt of the rescue medication or disallowed medication. Patients who did not experience minimal symptoms during the assessment period also were censored at the last assessment time point.

For time-to-event analyses, comparison of patients treated with rhC1INH and placebo was conducted by a log-rank test, stratified by primary attack location. The median time to an event (with 95% confidence interval) was presented for each treatment group. All statistical tests were performed 2-sided at the 5% level of significance. For categorical variables, the absolute counts and percentages of patients were presented. Efficacy data were analyzed using SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

Patient Disposition, Demographics, and Baseline Characteristics

Overall, 227 patients were screened; most patients not eligible for entry had functional C1INH higher than 50%. Seventy-five patients who presented with eligible acute HAE attacks were enrolled to receive study medication: 44 were randomized to rhC1INH and 31 were randomized to placebo. All 75 patients were included in the primary (intent-to-treat) efficacy analysis. One patient who was randomized to rhC1INH but did not receive the

Table 1

Location of primary eligible attack, attack severity at baseline, and use of rescue or disallowed concomitant medications

	rhC1INH (n = 44)	Placebo (n = 31)
Primary attack location, n (%) ^a		
Peripheral	19 (44)	14 (45)
Abdominal	16 (37)	12 (39)
Facial	6 (14)	2 (6)
Oropharyngeal-laryngeal	2 (5)	3 (10)
Overall severity VAS score at baseline for primary attack location		
Mean (SD)	73.5 (14.13)	77.3 (12.61)
Range	50–100	49–100
n	43 ^b	31
Use of rescue or disallowed concomitant medication before beginning of relief, n (%)	4 (9)	11 (35)

Abbreviations: rhC1INH, recombinant human C1 inhibitor; VAS, visual analog scale.

^aFor patients with more than 1 eligible attack location, the primary attack location was defined as the eligible location with the highest Overall Severity VAS score at baseline.

^bOne patient (randomized to rhC1INH) did not receive study medication and is not included in the summary table.

study drug was not included in the safety analysis. Patient given rhC1INH withdrew consent approximately 6 weeks after randomization and did not complete subsequent visits.

Patient disposition, key demographics, and HAE attack frequency are summarized by treatment group in Figure 1. Patient demographics and baseline characteristics were generally similar between treatment groups.

The primary attack locations for each patient, attack severity at baseline based on the VAS score, and the use of rescue or disallowed concomitant medications are summarized by treatment group in Table 1. Attack severity was similar in the 2 groups (rhC1INH 73.5 vs placebo 77.3). The most common primary attack locations in the 2 groups (rhC1INH vs placebo) were peripheral (44% vs 45%) and abdominal (37% vs 39%). Thirty-five percent of patients in the placebo group (11 of 31) vs 9% of patients in the rhC1INH group (4 of 44) received rescue medications or disallowed concomitant medications before the beginning of relief.

Time to Onset of Sustained Relief from Symptoms at the Primary Attack Location

The primary efficacy end point, time to onset of sustained relief from symptoms at the primary attack location, based on the TEQ, was significantly shorter in patients treated with rhC1INH (90 minutes) compared with patients treated with placebo (152 minutes, $P = .031$; Table 2, Fig 2A).

Multiple sensitivity analyses of the TEQ-based primary efficacy end point supported the results of the primary efficacy analysis, demonstrating significantly shorter times to onset of sustained relief from symptoms in patients treated with rhC1INH compared with patients treated with placebo. For example, when time to onset of relief was set to 24 hours for patients who received rescue medication or a disallowed concomitant medication to adjust for relief that might have been provided by those medications, time to onset of sustained relief from symptoms was significantly shorter for rhC1INH than for placebo (90 vs 334 minutes, $P = .01$; Table 2, Fig 2B). To evaluate whether the TEQ could discriminate clinically meaningful improvement in symptoms, the stringency of the end point was increased to require a response of “better” or “much better” to TEQ question 1 (ie, excluding responses of “a little better”). In this sensitivity analysis, time to onset of sustained relief from symptoms was significantly shorter in patients treated with rhC1INH compared with patients treated with placebo (122 vs 304 minutes, $P = .001$; Table 2). This result suggests that the primary

Table 2

Time to beginning of relief of symptoms at the primary attack location

Time to beginning of relief of symptoms (min)	Median (95% CI)		P value ^c
	rhC1INH (n = 44)	Placebo (n = 31)	
Based on TEQ ^a	90 (61–150)	152 (93 to —)	.031
Onset of relief set to 24 h for patients who received rescue or disallowed concomitant medication ^a	90 (61–150)	334 (105–1,440)	.010
Onset of relief based on response of “better” or “much better” required to TEQ question 1 ^a	122 (90–180)	304 (150 to —)	.001
Based on VAS score decrease ≥ 20 mm ^b	75 (60–105)	303 (81–720)	.003
Based on ISs decrease ≥ 1	60 (49–75)	105 (75 to —)	<.001

Abbreviations: —, not estimable; CI, confidence interval; IS, Investigator Score; rhC1INH, recombinant human C1 inhibitor; TEQ, Treatment Effect Questionnaire; VAS, visual analog scale.

^aBased on TEQ questions 1 and 2, with persistence.

^bBased on Overall Severity VAS score, with persistence.

^cP value was calculated from a log-rank test stratified by primary attack location (2-sided at $\alpha = 5\%$ level of significance).

TEQ-based end point was sensitive to small changes in patient symptoms, especially in placebo-treated patients, given the difference in median times to onset of relief in this sensitivity analysis compared with the TEQ-based primary efficacy analysis.

Consistent with the results of the primary TEQ-based end-point analysis, time to onset of sustained relief from symptoms based on the VAS score was significantly shorter in patients treated with rhC1INH compared with patients treated with placebo (75 vs 303 minutes, $P = .003$; Table 2). Time to onset of sustained relief from symptoms based on the IS also was significantly shorter in patients treated with rhC1INH than in patients treated with placebo (60 vs 105 minutes, $P < .001$; Table 2).

Recurrence of attack symptoms within 24 hours was seen in 1 (3%) of 31 patients in the rhC1INH group and 4 (27%) of 15 patients in the placebo group.

Time to Minimal Symptoms at All Attack Locations

Time to minimal symptoms at all attack locations, based on the TEQ, was shorter in patients treated with rhC1INH (303 minutes) compared with patients treated with placebo (483 minutes); this difference was not statistically significant ($P = .078$; Table 3). Time to minimal symptoms at all attack locations, based on the VAS score, was significantly shorter in patients treated with rhC1INH compared with patients treated with placebo (240 vs 362 minutes, $P = 0.005$; Table 3). Similar results were obtained for analysis of time to minimal symptoms based on the IS ($P = 0.047$; Table 3).

Safety and Tolerability

Treatment emergency adverse events (TEAEs) are summarized by treatment group in Table 4. Two rhC1INH-treated patients experienced TEAEs of mild severity (procedural headache, fibrin D-dimer increase) that commenced within 4 hours after dosing. One patient experienced mild procedural headache, mild skin burning sensation, and moderate back pain at 15 minutes, 45 minutes, and 1 day, respectively, after rhC1INH administration; these TEAEs were assessed as possibly related to study drug. No other TEAEs were assessed as related to study drug. The percentages of patients experiencing TEAEs that commenced within 72 hours or up to 97 days (protocol-specified analysis period) after dosing were smaller in patients who received rhC1INH as double-blinded and/or open-label rescue medication than in patients who received treatment only with placebo. There were no deaths and no discontinuations from TEAEs. Most reported TEAEs were of mild or moderate severity; 3 patients

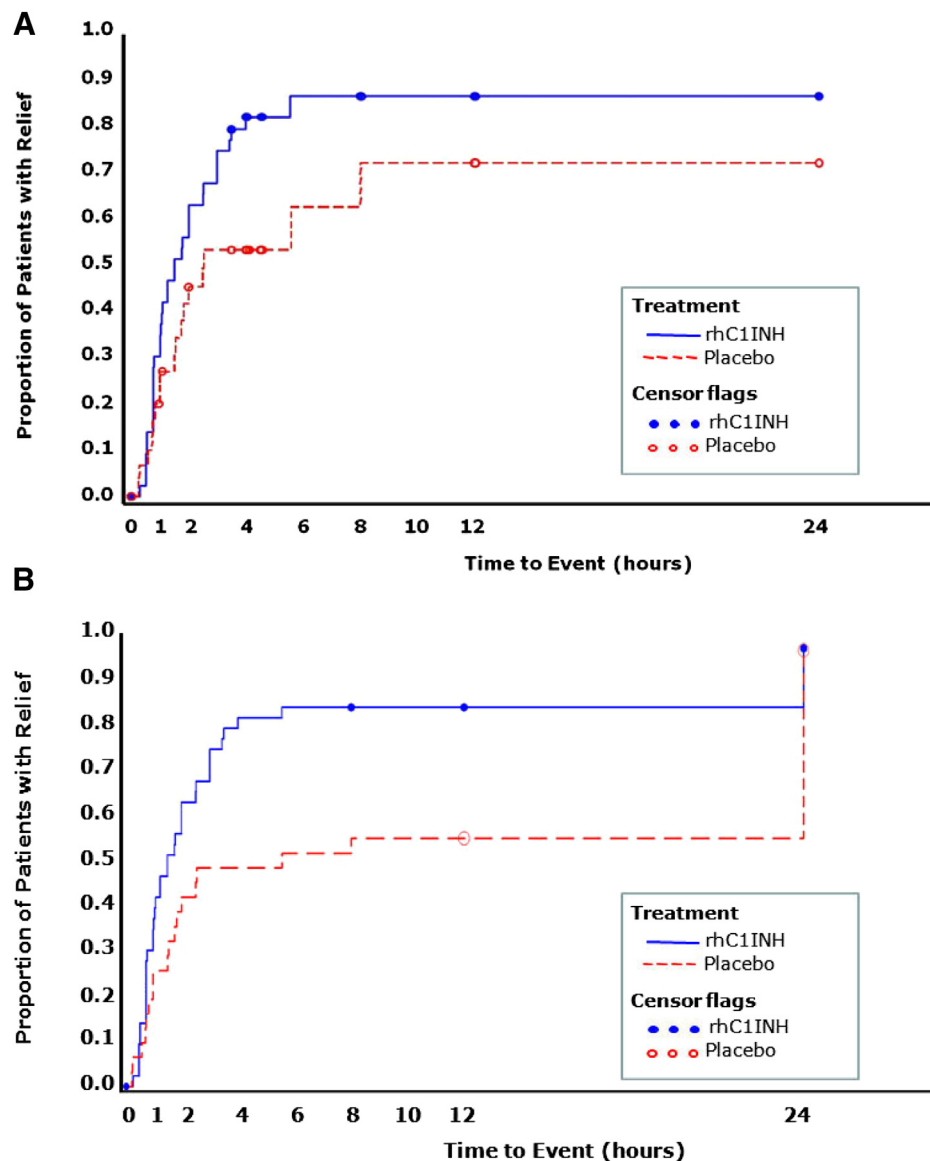


Figure 2. Kaplan-Meier plot of time to onset of sustained relief from symptoms at the primary attack location (A) based on the Treatment Effect Questionnaire and (B) based on the Treatment Effect Questionnaire setting patients who received rescue or disallowed concomitant medication to 24 hours. rhC1INH, recombinant human C1 inhibitor.

experienced severe TEAEs (urinary tract infection and abdominal hernia in the rhC1INH group; sinus congestion in the placebo group), which were judged by the investigator not to be related to study medication. One rhC1INH-treated patient experienced a serious

TEAE (abdominal hernia) approximately 79 days after dosing. The most common TEAEs that commenced within 72 hours after dosing were in the respiratory, thoracic, and mediastinal disorder and gastrointestinal disorder organ system classes (Table 5).

Table 3
Time to minimal symptoms at all attack locations

Time to minimal symptoms (min)	Median (95% CI)		P value ^c
	rhC1INH (n = 44)	Placebo (n = 31)	
Based on TEQ ^a	303 (240–720)	483 (300–1,440)	.078
Based on all VAS scores <20 mm ^b	240 (177–270)	362 (240 to —)	.005
Based on all ISs ≤1	330 (270–361)	— (300 to —)	.047

Abbreviations: —, not estimable; CI, confidence interval; IS, Investigator Score; rhC1INH, recombinant human C1 inhibitor; TEQ, Treatment Effect Questionnaire; VAS, visual analog scale.

^aBased on TEQ question 3.

^bBased on Overall Severity VAS score.

^cP value was calculated from a log-rank test stratified by primary attack location (2-sided at $\alpha = 5\%$ level of significance).

Table 4
Overview of treatment emergency adverse events

	rhC1INH (n = 56), ^b n (%)	Placebo (n = 18), ^c n (%)
Patients with ≥1 TEAE		
TEAE commencing within 72 h after dosing	4 (7)	4 (22)
TEAE commencing within 97 d after dosing ^a	18 (32)	10 (56)
Serious TEAE	1 (2)	0
Fatal TEAE	0	0
Related TEAE	1 (2)	0

Abbreviations: rhC1INH, recombinant human C1 inhibitor; TEAE, treatment emergency adverse event.

^aProtocol-specified follow-up period.

^bIncludes patients treated with rhC1INH as double-blinded and/or open-label rescue medication.

^cPatients treated only with placebo.

Table 5

Treatment emergency adverse events commencing within 72 hours after dosing

MedDRA preferred term	rhC1INH (n = 56), ^b n (%)	Placebo (n = 18), ^c n (%)
Sinus congestion	0	1 (6)
Sneezing	1 (2)	0
Vasomotor rhinitis	0	1 (6)
Diarrhea	0	1 (6)
Dyspepsia	0	1 (6)
Procedural headache ^a	1 (2)	0
Fibrin D-dimer increased	1 (2)	0
Back pain ^a	1 (2)	0
Lipoma	1 (2)	0
Skin burning sensation ^a	1 (2)	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities Version 15.0; rhC1INH, recombinant human C1 inhibitor.

^aEvents experienced by the same patient and all judged by the investigator to be related to study medication.

^bIncludes patients treated with rhC1INH as double-blinded and/or open-label rescue medication.

^cPatients treated only with placebo.

There were no clinically significant changes from baseline to any post-baseline time points in median hematology, biochemistry, coagulation, urinalysis, or vital signs values, and no patients had clinically significant abnormal electrocardiographic findings. No patients developed neutralizing antibodies to C1INH, and no anaphylactic events were reported. Confirmed nontreatment emergency anti-rhC1INH IgM was detected in 1 patient receiving placebo. Confirmed anti–host-related impurity antibodies were detected in 8 patients treated with rhC1INH (6 treatment emergencies) and 3 patients treated with placebo only (1 treatment emergency). In all cases, immunogenic responses were transient and sporadic, and medical review confirmed no temporal relation between the presence of antibodies and AEs. Importantly, no thrombotic events were reported for any patients. Consistent with the presence of an ongoing HAE attack,²⁰ median D-dimer concentrations were elevated at baseline and at 2 hours after dosing in the 2 treatment groups; by day 7, these values had decreased in the 2 groups.

Discussion

Recombinant human C1INH was developed as an alternative to pdC1INH for the treatment of acute angioedema attacks in patients with HAE. The present study affirms the efficacy of rhC1INH 50 IU/kg, together with its favorable safety profile, in a larger population of patients experiencing HAE attacks compared with previous studies. The study demonstrated that rhC1INH produces a significant and clinically meaningful decrease in time to onset of sustained relief from symptoms compared with placebo. These findings are consistent with the results of the prior randomized controlled studies conducted with rhC1INH in patients experiencing HAE attacks.⁸

Consistent with clinical experience, the present study enrolled patients with HAE who were experiencing moderate to severe angioedema attacks across a real-world distribution of attack locations (peripheral, abdominal, facial, oropharyngeal-laryngeal), unlike prior studies with pdC1INH products that enrolled primarily patients with abdominal or facial attacks.^{16,17} Inclusion of patients with any affected location is important given recent treatment guidelines advising early treatment of all attacks, regardless of location or severity.^{21–23}

Time to onset of sustained relief from symptoms was significantly shorter in patients treated with rhC1INH than in patients treated with placebo, regardless of the instrument (TEQ, VAS, or IS) used to assess efficacy. Similarly, time to minimal symptoms was numerically shorter in patients treated with rhC1INH when

measured using the TEQ and was significantly shorter when measured using the VAS compared with patients treated with placebo. Thus, across all 3 randomized controlled studies conducted with rhC1INH in patients with HAE, consistent benefit was seen when efficacy was assessed using the validated VAS instrument. Collectively, these 3 studies provide strong evidence for the efficacy of rhC1INH in a large sample of representative patients with HAE across multiple assessment tools and multiple end points. These findings also are consistent with the conclusion, based on a review of efficacy and pharmacokinetic data from prior controlled trials with rhC1INH and pdC1INH, that efficacy is dose dependent and is optimal at doses of at least 50 IU/kg.¹⁵

This study represents the first use of the TEQ in a clinical study of HAE treatment. The TEQ and VAS evaluation instruments appear to differ somewhat in their ability to discriminate changes in HAE symptomatology. Although median times to beginning of persistent relief from symptoms were similar in rhC1INH-treated patients using the TEQ and the VAS, these median times were longer in placebo-treated patients when measured by the VAS score than by the TEQ. The exploratory analysis in which the stringency of the TEQ-based end point was increased (Table 2) suggested that the TEQ is more sensitive to small changes in symptom severity than the VAS and, hence, may have limited discriminatory capabilities, especially in placebo-treated patients. Regardless of the definition of improvement or assessment measurement used, rhC1INH was demonstrated to be superior to placebo in achieving beginning of relief from symptoms across the 3 controlled studies.⁸

Of the rhC1INH-treated patients who achieved beginning of persistent relief from symptoms within 4 hours of rhC1INH treatment, 1 patient (3%) had a recurrence of symptoms within 24 hours. This was the only case of recurrence of symptoms after initial improvement within 24 hours after dosing across the entire rhC1INH clinical development program. By comparison, relapse rates of 10% to 31% have been reported for other acute treatments for angioedema attacks in patients with HAE.^{24–28}

The present study reaffirms previous observations on overall safety of rhC1INH in the treatment of angioedema attacks based on an evaluation of clinical events and clinical laboratory parameters. Importantly, after a single administration of rhC1INH, there were no thrombotic or anaphylactic events in patients treated with rhC1INH, no patients developed neutralizing antibodies to rhC1INH, and antibodies against C1INH and host-related impurities were infrequent, consistent with findings in prior rhC1INH clinical trials.^{8–10,12,29} Evaluation of the safety and immunogenicity of repeated rhC1INH administration in this population of patients from an open-label extension study remains ongoing. However, the authors' previous experience in open-label studies suggests that treatment with rhC1INH for repeated attacks is safe and efficacious.^{9,10}

In conclusion, in patients with HAE experiencing angioedema attacks, rhC1INH treatment provided rapid and sustained symptom improvement, with a markedly low rate of symptom recurrence, compared with placebo. The rhC1INH treatment effect was statistically significant and clinically meaningful, with an overall positive safety profile. The first available recombinant human C1INH product, rhC1INH provides a clinically effective treatment for angioedema attacks without the concerns of availability and risks of donor plasma supply. The present study confirms previous evidence supporting the use of rhC1INH as a therapeutic option for the management of HAE attacks.

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Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2013.12.004>.

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