

Efficacy of recombinant human C1 esterase inhibitor for the treatment of severe hereditary angioedema attacks

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ABSTRACT

Background: Severe attacks of hereditary angioedema (HAE) are debilitating and potentially life threatening, and can increase anxiety and the use of medical resources.

Objective: This post hoc assessment evaluated recombinant human C1 esterase inhibitor (rhC1-INH) used to treat acute severe HAE attacks.

Methods: In a double-blind, randomized-controlled trial (RCT), patients with an HAE attack (baseline visual analog scale score of ≥ 50 mm, with severe attacks defined as ≥ 75 mm) were randomly assigned to receive rhC1-INH (50 IU/kg for patients who weighed < 84 kg; 4200 IU for patients who weighed ≥ 84 kg) or placebo. Also, in an open-label extension (OLE) study of rhC1-INH, oropharyngeal-laryngeal attacks were analyzed. Rescue therapy with rhC1-INH 50 IU/kg (≤ 4200 IU) was permitted after 4 hours or for life-threatening symptoms (in the RCT) or after 1 hour (in the OLE study). The primary end point measured the time to the beginning of symptom relief by using the Treatment Effects Questionnaire.

Results: Of 75 adults in the RCT, 43 had severe attacks and received either rhC1-INH ($n = 24$) or placebo ($n = 19$). The median (95% confidence interval) time to the onset of symptom relief totaled 90.0 minutes (95% confidence interval, 47.0–120.0 minutes) versus 334.0 minutes (95% confidence interval, 105.0 to not calculable minutes; hazard ratio, 2.5; $p = 0.02$), for rhC1-INH and placebo, respectively. Open-label rhC1-INH rescue therapy was administered to 1 of 24 in the rhC1-INH group (4.2%) and 10 of 19 in the placebo group (52.6%). During the OLE study, the median onset of symptom relief with rhC1-INH for eight oropharyngeal-laryngeal HAE attacks was 69.0 minutes (95% confidence interval, 59.0–91.0 minutes).

Conclusion: In the current study, rhC1-INH was efficacious in resolving severe HAE attacks, including oropharyngeal-laryngeal attacks. The rhC1-INH rescue treatment rapidly improved symptoms for patients who received placebo and who experienced worsening or sustained symptoms.

(Allergy Asthma Proc 38:456–461, 2017; doi: 10.2500/aap.2017.38.4088)

Hereditary angioedema (HAE) is a rare but serious genetic disorder characterized by subcutaneous or submucosal edema of the extremities, abdomen,

genitourinary tract, face, larynx, or oropharynx.^{1,2} HAE attacks may persist for up to 5 days, although more typically, the natural history of HAE attacks is characterized by worsening of symptoms during the initial 24-hour period and resolution within 72 hours.¹ HAE attacks induce pain and discomfort, severely affect patients' quality of life,^{3,4} and contribute to anxiety and depression.⁵ Frequent attacks reduce patients' ability to perform daily life activities⁵ and increase utilization of health resources.⁴ The frequency and severity of HAE attacks are variable and unpredictable; however, the risk of recurrence is high and compounds the adverse impact of the disorder on overall patient health.⁶ In addition, although laryngeal attacks are fairly rare,^{3,5,7} they may cause asphyxiation,⁸ which, especially in severe cases, may be life threatening. HAE is an autosomal dominant genetic disorder caused by mu-

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Presented, in part, at the American College of Allergy, Asthma & Immunology 2014 Annual Scientific Meeting, November 6–10, 2014, Atlanta, Georgia, and at the 2016 HAE Global Conference in Madrid, Spain, May 19–22, 2016

Funding for the trial was provided by Pharming Technologies BV, Leiden, The Netherlands. H. H. Li, A. Reshef, and J.W. Baker have received research grants from Pharming Technologies. A. Reshef has served on the speakers' bureau for Pharming Technologies. J. R. Harper and A. Relan are employees of Pharming Healthcare Inc.

Technical editorial and medical writing support was provided, under the direction of the authors, by Mary Beth Moncrief, Ph.D., and Jill Gee, Ph.D., Synchrony Medical Communications, LLC, West Chester, Pennsylvania. Funding for this support was provided by Salix Pharmaceuticals, Bridgewater, New Jersey, and Pharming Technologies BV, Leiden, The Netherlands

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Supplemental data available at www.IngentaConnect.com

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Published online September 5, 2017

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tations within the C1 esterase inhibitor (C1-INH) gene (serpin family G member 1); these mutations result in low levels of functional C1-INH, which allows overproduction of bradykinin.² Therefore, treatments for HAE are designed to supplement C1-INH or inhibit bradykinin.

Recombinant human C1-INH (rhC1-INH) (Ruconest; Pharming Technologies B.V., Leiden, The Netherlands) is a recombinant product isolated from the milk of transgenic rabbits,⁹ which is approved for the treatment of acute HAE attacks in adolescents and adults in the United States, the European Union, and several other countries. rhC1-INH acts by restoring plasma levels of functional C1-INH activity.¹⁰ The potential risks of blood-borne infections are minimized by the transgenic platform used for rhC1-INH production.⁹ Several randomized and open-label clinical studies in patients with HAE attacks have demonstrated that rhC1-INH can effectively shorten the time to the beginning of sustained symptom relief.^{6,9,11–13} The efficacy and safety of rhC1-INH was assessed in both a randomized controlled trial (RCT) and an open-label extension (OLE) study.

In the RCT, rhC1-INH administration in patients obtained a median time to the beginning of sustained symptom relief of 90.0 minutes in the primary attack location compared with 152.0 minutes in patients who received placebo ($p = 0.03$).⁹ In the OLE study, the median time to the beginning of symptom relief in five subsequent attacks was 75.0 minutes (95% confidence interval [CI], 69.0–89.0 minutes).¹³ In the original RCT cohort, patient enrollment was based on inclusion criteria that encompassed the overall severity score of ≥ 50 mm on the visual analog scale (VAS) at presentation and at the time of dosing.⁹ However, little is known about the efficacy of rhC1-INH in patients with severe symptoms during HAE attacks. The current *post hoc* analysis of data from the aforementioned studies evaluated the efficacy of rhC1-INH in a subgroup of patients with the most-severe HAE attacks.

METHODS

This was a *post hoc* analysis of a multicenter study, which was composed of a double-blind RCT and an associated OLE study (ClinicalTrials.gov identifier NCT01188564). The patient populations and study designs were previously published.^{9,13} Institutional review board approval was obtained for each study (Supplemental Appendix). Briefly, in the RCT, patients ≥ 13 years of age (United States and Canada) or ≥ 18 years of age (South Africa, Italy, Israel, Romania, Poland, Hungary, Bulgaria, Macedonia, and Serbia) who had an established diagnosis of HAE (*i.e.*, baseline plasma C1-INH activity $< 50\%$ of normal, excluding acquired angioedema) were included in the study. Eligible HAE attacks had to meet the following criteria: a peripheral (extremities), abdominal, facial, and/or oropharyngeal-laryngeal location; an

attack initiated within 5 hours of presentation to the site; severity ≥ 50 mm by VAS score (1–100 mm) at presentation and before treatment administration; and a reduction of < 20 mm in overall severity between presentation and treatment administration. All the patients who participated in the RCT were eligible to enter the OLE study.

In the RCT, the patients who experienced an eligible HAE attack were randomly assigned, 3:2, to receive intravenous rhC1-INH (50 IU/kg for patients who weighed < 84 kg; 4200 IU for patients who weighed ≥ 84 kg) or placebo (saline solution). Patients with significant pain, discomfort, or disability related to their attacks, who did not experience symptom relief within 4 hours of initial treatment, and who had oropharyngeal-laryngeal symptoms received open-label rhC1-INH 50 IU/kg (≤ 4200 IU) as rescue medication. The patients in the OLE study received a single dose of intravenous rhC1-INH (50 IU/kg for patients who weighed < 84 kg; 4200 IU for patients who weighed ≥ 84 kg). In that study, a second dose of rhC1-INH was permitted beginning after 1 hour, unless symptoms had markedly worsened, after the initial drug administration at the discretion of the investigator.

HAE attack severity was assessed in the RCT by using a VAS score (range, 0 mm [no symptoms at all] to 100 mm [extremely disabling symptoms]). For the current analysis, severe attacks were defined by a VAS score of ≥ 75 mm. The 75-mm minimum VAS score was selected because it is the mid point between 50 mm (the minimum HAE VAS score at presentation for eligibility in the original study⁹) and 100 mm (maximum possible VAS score). In addition, this reflected the mean baseline HAE VAS severity score of 75 for the overall patient population in the original study (data on file, Pharming Healthcare Inc., Bridgewater, NJ). Symptom improvement was also assessed by using the Treatment Effect Questionnaire (TEQ).⁹ The TEQ was performed every 15 minutes for 2 hours after treatment and then every 30 minutes for 4 hours (*i.e.*, 6 hours total). The primary end point of the analysis was the time to the beginning of symptom relief (*i.e.*, improvement on the first two of the three questions of the TEQ at two consecutive assessments at the primary attack location). The time to onset of symptom relief was also assessed by using the VAS (*i.e.*, a ≥ 20 -mm decrease from the baseline score at two consecutive assessments).

Patients in the RCT were eligible for inclusion in the current *post hoc* analysis if they were randomly assigned to treatment and if the HAE attack met the level of attack severity (a VAS score of ≥ 75 mm) just before administration of the study drug. Patients in the OLE study were included in this *post hoc* analysis if they had an oropharyngeal-laryngeal attack as the primary HAE attack location and were treated with rhC1-INH. Between-group comparisons of the time to the event data were performed by using a log-rank test. During the RCT, if a patient received rescue medication, then the time to the

Table 1 Patient demographics and baseline characteristics in the RCT

Characteristic	Patients with Severe Attacks	
	rhC1-INH 50 IU/kg (n = 24)	Placebo (n = 19)
Age, mean (range), y	39.6 (20–67)	38.8 (18–62)
Sex, no. (%)		
Men	8 (33.3)	7 (36.8)
Women	16 (66.7)	12 (63.2)
Race, no. (%)		
White	23 (95.8)	19 (100)
Black	1 (4.2)	0
HAE attack location, no. (%)		
Abdominal	10 (41.7)	6 (31.6)
Facial	1 (4.2)	2 (10.5)
Oropharyngeal-laryngeal	1 (4.2)	2 (10.5)
Peripheral	12 (50.0)	9 (47.4)

RCT = Randomized controlled trial; rhC1-INH = recombinant human C1 esterase inhibitor; HAE = hereditary angioedema.

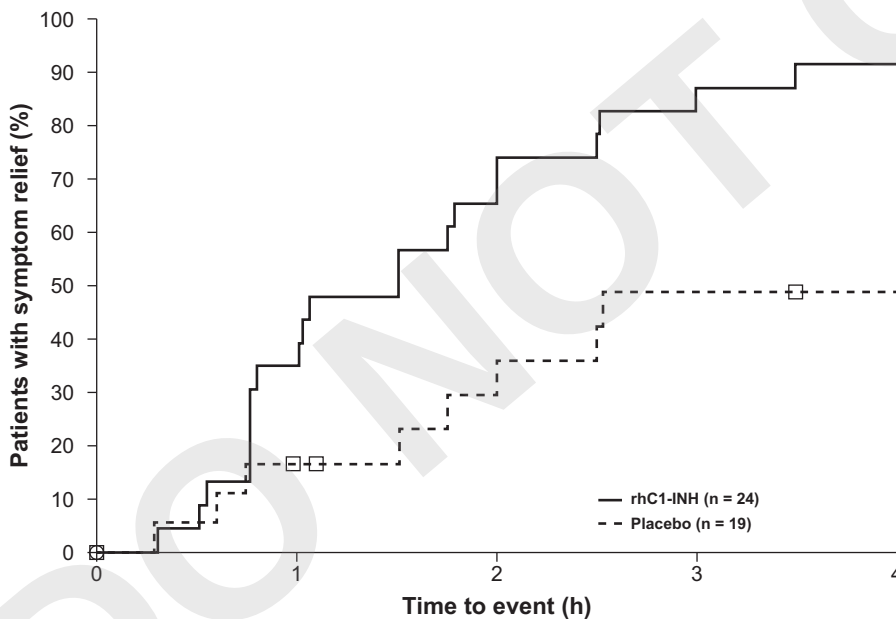


Figure 1. A Kaplan-Meier plot of the time to the beginning of symptom relief, assessed by using the TEQ, in patients with severe HAE attacks. Open circles (rhC1-INH) or squares (placebo) indicate censor flags: if a patient received rescue medication, then the time to the beginning of relief from symptoms was censored at the time of rescue medication administration (i.e., excluded from further efficacy analyses). TEQ = Treatment Efficacy Questionnaire; HAE = hereditary angioedema; rhC1-INH = recombinant human C1 esterase inhibitor.

beginning of relief from symptoms was censored at the time of rescue medication administration. Because life-threatening attacks were not eligible for randomization, a separate analysis was conducted for oropharyngeal-laryngeal attacks treated during the OLE study. Statistical tests were two sided at the 5% level of significance.

RESULTS

Patient Demographics, Disposition, and Characteristics

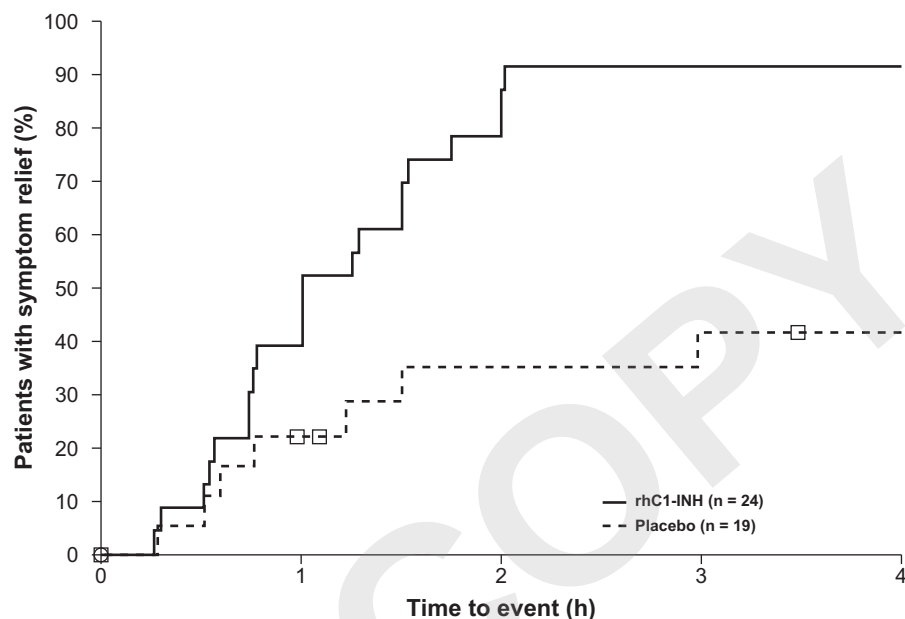
Demographic and baseline characteristics and disposition of the original patient cohorts are reported elsewhere.^{9,13} Of the 75 patients who were eligible for enrollment in the RCT (rhC1-INH, *n* = 44; placebo, *n* = 31), 43

patients (57.3%), all adults, met the criteria for severe HAE attacks (rhC1-INH, *n* = 24; placebo, *n* = 19). Patient demographics and characteristics of these two treatment populations were similar (Table 1). Primary attack locations involved the peripheral extremities and the abdomen, with no observed differences between the groups. Of the 44 patients who participated in the OLE study, 8 patients (7 women; ages, 23–59 years) experienced eight oropharyngeal-laryngeal attacks as the primary attack location and were included in the analysis.¹³

Patient-Reported Outcomes: TEQ

In the RCT, all 43 patients were included in the primary efficacy analysis. In one patient, who was not

Figure 2. A Kaplan-Meier plot of the time to achieve a ≥ 20 -mm improvement from baseline in the VAS score. Open circles (rhC1-INH) or squares (placebo) indicate censor flags: if a patient received rescue medication, then the time to the beginning of relief from symptoms was censored at the time of rescue medication administration. VAS = Visual analog scale; rhC1-INH = recombinant human C1 esterase inhibitor.



dosed, only the VAS score at presentation was used. The median time to the beginning of symptom relief for patients with severe HAE attacks was significantly shorter with rhC1-INH (90.0 minutes [95% CI, 47.0–120.0 minutes]) than with placebo (334.0 minutes [95% CI, 105.0 to not calculable minutes]; $p = 0.02$) (Fig. 1). By the end of 24 hours of follow-up, 91.7% (22/24) and 47.4% (9/19) of the patients had achieved relief of symptoms in the rhC1-INH and placebo groups, respectively, and these data included those patients who received rescue medication (see Rescue Medication Use). Overall, the reduction in median time to the onset of symptom relief significantly favored rhC1-INH ($p = 0.02$) (Fig. 1). Of patients randomly assigned to receive rhC1-INH, $\sim 90\%$ achieved ≥ 20 -mm decrease in VAS score within 4 hours after treatment (Fig. 2). By contrast, only $\sim 40\%$ of patients randomly assigned to receive placebo experienced a ≥ 20 -mm decrease in VAS score. In comparison, the separate analysis for oropharyngeal-laryngeal attacks in patients treated with open-label rhC1-INH during the OLE study showed that, for the eight HAE oropharyngeal-laryngeal attacks observed, the median time to the beginning of symptom relief was 69.0 minutes (95% CI, 59.0–91.0 minutes) (Fig. 3).

Rescue Medication Use

During the RCT, rescue medication was provided for patients who either did not experience symptom relief within 4 hours of initial treatment or experienced life-threatening symptoms (Table 2). All the patients received open-label rhC1-INH as rescue medication; no additional rescue interventions were necessary. Among those who required rescue medication, the median VAS score at

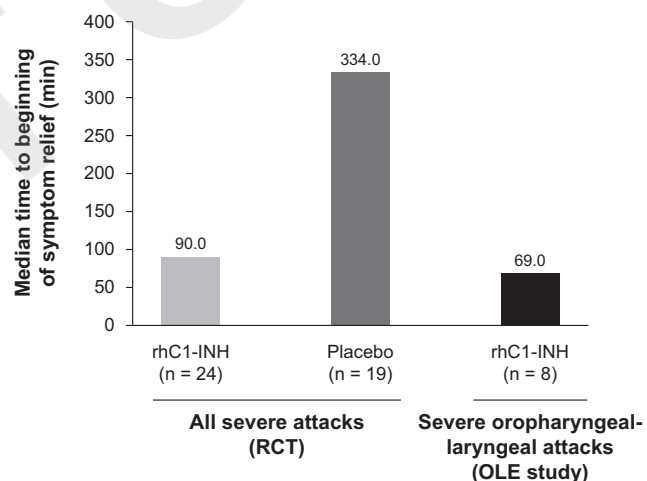


Figure 3. The time to the beginning of symptom relief in all severe attacks or severe oropharyngeal-laryngeal attacks only. OLE = Open-label extension; RCT = randomized controlled trial; rhC1-INH = recombinant human C1 esterase inhibitor.

baseline equaled 84 mm (range, 75–99 mm). Rescue medication (*i.e.*, open-label rhC1-INH) was required in a higher percentage of patients randomly assigned to receive placebo (10/19 [52.6%]) compared with rhC1-INH (1/24 [4.2%]). Within the placebo group, the use of rescue medication was necessitated by the development, persistence, or worsening of airway symptoms ($n = 3$); persistence of symptoms ($n = 5$); and worsening of the nonairway symptoms ($n = 2$). One patient in the rhC1-INH group required rescue medication because of persistent facial symptoms. The median time to the beginning of symptom relief after receiving rhC1-INH as rescue medication was 59.5 minutes (range, not calculable to 240 minutes).

Table 2 Summary of rescue medication use outcomes

Treatment Group	Time from Attack Onset to Presentation in Clinic, min	VAS at Baseline, mm	Symptom Course Postdose	Time to Rescue Medication Postdose, min	Time to Onset of Symptom Relief After rhC1-INH Rescue, min
Placebo	150	87	New oropharyngeal-laryngeal symptoms developed at 30 min, with worsening by 60 min	75	35
Placebo	190	76	No improvement in hand and foot angioedema symptoms by 4 hr	268	68
Placebo	228	88	Worsening of hand and arm angioedema symptoms by 4 hr	253	91
Placebo	240	99	No improvement of hand angioedema symptoms by 4 hr	249	51
Placebo	185	86	Worsening oropharyngeal-laryngeal symptoms by 60 min	71	77
Placebo	140	75	Improvement in abdominal symptoms at 2.5 hr, then worsening beginning at 4.5 hr	340	140*
Placebo	150	77	No improvement of abdominal symptoms by 4 hr	283	50
Placebo	150	84	No improvement of arm angioedema by 4 hr	278	25
Placebo	145	83	No improvement of facial angioedema by 4 hr	300	30
Placebo	160	97	No improvement of oropharyngeal-laryngeal symptoms by 4 hr	240	240
rhC1-INH	250	78	Persistent facial symptoms by 4 hr	246	103

VAS = Visual analog scale; rhC1-INH = recombinant human C1 esterase inhibitor.

*The patient achieved time to onset of relief of symptoms before administration of rescue medication.

DISCUSSION

Symptoms of HAE adversely affect general health and patient functionality in daily activities, both during and between attacks.⁵ Patients with HAE attacks who experience severe symptoms (*e.g.*, pain) are particularly prone to work or school absenteeism, reduced productivity, and increased utilization of health care resources.⁴ The significant impact on patients' quality of life and the potential risk of asphyxiation related to laryngeal attacks indicate that prompt and effective treatment for severe attacks is highly desirable for patients who live with HAE.

To our knowledge, this was the first time that the efficacy of an HAE therapeutic was specifically assessed in patients who experienced severe attacks across an array of primary attack locations using a validated VAS scale.^{6,14} Our findings in this severely affected subgroup of patients support previous observations that rhC1-INH effectively reduced the time to the beginning of symptom relief compared with placebo.

This finding was consistent with the overall results of the phase III RCT population (the original cohort), in which the time to onset of sustained symptom relief was significantly shorter with rhC1-INH (90.0 minutes) compared with placebo (152.0 minutes; $p = 0.03$).⁹ In addition, ~90% of the patients treated with rhC1-INH achieved a ≥ 20 -mm (VAS) improvement from baseline ~2 hours after the dose in the current study, and this degree of improvement has been shown to be a clinically meaningful difference.^{6,15,16}

The results of rhC1-INH in severe HAE attacks were also consistent with data from a subgroup analysis of two other studies, which demonstrated that rhC1-INH 100 IU/kg or 50 IU/kg reduced the median time to the beginning of symptom relief (68.0 minutes [95% CI, 60.0–123.0 minutes] and 136.0 minutes [95% CI, 29.0–250.0 minutes], respectively) compared with placebo (495.0 minutes [95% CI, 243.0–720.0 minutes]) in patients with severe attacks (defined as a score of 4 on a

6-point scale that ranged from 0 [no symptoms] to 5 [life-threatening symptoms]).⁶ Analysis of these data, taken together, underscored the efficacy of rhC1-INH in patients who experienced severe attacks. Whereas acute attacks of HAE are most frequently experienced in the subcutaneous tissue (*i.e.*, extremities) and in the submucosa of the intestines (*i.e.*, abdominal attacks), assessing the effect of rhC1-INH on severe oropharyngeal-laryngeal attacks is critical. Among the eight HAE attacks in the OLE study in which the oropharyngeal-laryngeal site was the primary attack location, rhC1-INH treatment was associated with a rapid onset of effect (median, 69.0 minutes).

Although the current study was not designed to determine the efficacy of treatment for recurrent acute episodes, the efficacy of rhC1-INH for recurrent attacks has already been reported.¹³ In that study, the median time to the beginning of symptom relief for the first five episodes as measured by the TEQ was 75.0 minutes (95% CI, 69.0–89.0 minutes), with a range of 62.5 minutes (95% CI, 48.0–90.0 minutes) to 134.0 minutes (95% CI, 75.0–150.0 minutes). There were 11 cases of rescue medication use in the current study, 10 patients in the placebo group (90.9%) and 1 patient in the rhC1-INH group (9.1%). All the patients from the placebo group who received rescue rhC1-INH treatment experienced symptom relief after the first rhC1-INH dose, and no other rescue medication was needed.

The interpretation of the data in this analysis was limited by the *post hoc* nature of the analysis. In addition, only adults met the criteria for severe HAE attacks in the RCT; therefore, no data for younger populations were available. Also, the OLE study included fewer patients than did the RCT. However, this analysis included a fairly large number of patients with severe HAE symptoms in the RCT ($n = 43$). Moreover, an array of primary attack locations was included, which aligns with real-world experiences (as opposed to studying a single attack location). Although the TEQ has not been validated among patients with HAE, the results of the current analysis concurred with data from the overall phase III study population, which demonstrated a significantly shorter time to the beginning of symptom relief with rhC1-INH compared with placebo when using both the TEQ and the VAS.

CONCLUSION

The current study supports the efficacy of rhC1-INH therapy for the treatment of acute severe HAE attacks; rhC1-INH reduced the time to the beginning of symptom relief compared with placebo, and the open-label data confirmed the efficacy of rhC1-INH for the treatment of oropharyngeal-laryngeal HAE attacks. Furthermore, rapid improvement after rhC1-INH rescue

treatment was also observed for patients who received placebo and who experienced worsening or sustained symptoms. Therefore, these data add to the overall efficacy and safety profile of rhC1-INH for the treatment of acute attacks of HAE.

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