



# Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial

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## ABSTRACT

**Background:** Hereditary angioedema (HAE) is a rare disease caused by *C1INH* gene mutations, which leads to a deficiency or dysfunction of C1 inhibitor (C1 INH), resulting in recurrent episodes of severe and potentially life-threatening edema.

**Objective:** To evaluate the efficacy and safety of repeat use of nanofiltered C1 esterase inhibitor (human) (C1 INH-nf) for the short-term treatment of HAE attacks.

**Methods:** In this open-label study, patients received C1 INH-nf, 1,000 U intravenously, for the treatment of HAE attacks. Efficacy end points included the proportion of attacks with unequivocal relief of the defining symptom within 1 and 4 hours after receiving study drug and time to beginning of relief of the defining symptom. Safety was monitored through adverse event reporting, vital signs measurements, and laboratory testing.

**Results:** A total of 113 patients were enrolled in the study from September 21, 2006, through March 31, 2009, and received 885 doses of C1 INH-nf. A total of 609 HAE attacks were treated with C1 INH-nf, and the numbers of attacks achieving unequivocal relief of the defining symptom within 1 and 4 hours after the start of the first dose were 412 (68%) and 529 (87%), respectively. Of 101 patients treated for an attack during the study period, 80 achieved unequivocal relief of their first attack within 4 hours after study medication (response rate, 79%); median time to the beginning of unequivocal relief was 0.75 hour. C1 INH-nf was safe and well tolerated.

**Conclusions:** This open-label study demonstrates the efficacy and safety of C1 INH-nf for short-term treatment of HAE attacks.

**Trial Registration:** [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00438815.

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## Introduction

Hereditary angioedema (HAE) is a rare autosomal-dominant disease caused by mutations in the *C1INH* gene, leading to functional C1 inhibitor (C1 INH) deficiency. In many patients, this is accompanied by a quantitative deficiency of C1 INH.<sup>1–5</sup> C1 INH plays an important role in regulation of vascular permeability; therefore, a defective *C1INH* gene can lead to severe angioedema. HAE is characterized by recurrent and unpredictable attacks of intense, localized edema that may involve the face, extremities, abdomen, or genitalia and can be painful, disabling, and life-threatening.<sup>4</sup> Angioedema of the airway may produce asphyxiation in patients who do not receive appropriate treatment.<sup>6</sup> Both type I HAE (reduced C1 INH production and function)<sup>3</sup> and type II HAE (normal or elevated C1 INH, but low functional levels)<sup>5</sup> present similarly.

Earlier studies evaluating C1 INH replacement therapy for short-term treatment of HAE attacks demonstrated favorable efficacy and safety.<sup>7–11</sup> This study evaluated the efficacy and safety of repeat use of nanofiltered C1 esterase inhibitor (human) (C1 INH-nf; CINRYZE, ViroPharma Incorporated, Exton, Pennsylvania) for the treatment of HAE attacks. It was an extension of a previous phase 3, double-blind, randomized trial demonstrating that C1 INH-nf significantly shortened the duration of attacks compared with placebo<sup>11</sup> and included patients who would have been excluded from the previous trial.

## Methods

### Study design

This prospective, open-label study was conducted at 29 centers in the United States. The clinical protocol, protocol amendments, and informed consent forms were reviewed and approved by an independent ethics committee/institutional review board for each investigative site. Patients 1 year or older who provided written informed consent (patient or parent or legal guardian) were eligible for the current study if they had completed participation in a previous randomized short-term treatment trial or routine prophylaxis trial with C1 INH-nf<sup>11</sup> or were enrolled but not randomized before study completion in the previous short-term treatment trial. Patients excluded from the previous trial for pregnancy or lactation, age younger than 6 years, narcotic addiction, or presence of C1 INH autoantibody were allowed in this open-label extension. In addition, patients could enroll in the study if they had a diagnosis of HAE based on low antigenic or functional C1 INH levels and a low C4 level, documented HAE-causing *C1INH* mutation, or diagnosis of HAE based on family history of HAE as determined by the principal investigator. Patients were excluded if they had a history of allergic reaction to C1 INH or other blood products, participated in another study within 30 days of enrollment, or received blood or blood product within 60 days of enrollment (other than C1 INH-nf).

Patients were to report to the study center for treatment within 4 hours after the onset of an angioedema attack. Patients received C1 INH-nf, 1,000 U by intravenous (IV) injection, which could be repeated after 60 minutes if the patient did not experience relief. Patients could be treated for attacks occurring at various body sites, including all laryngeal and moderate or severe gastrointestinal, facial, genitourinary, and extremity attacks. Patients could also receive C1 INH-nf, 1,000 U IV, for short-term prophylaxis before emergency or noncosmetic surgical or dental procedures.

Patients assessed posttreatment symptom relief every 15 minutes (up to 4 hours) or until achieving substantial relief of the defining symptom using the following descriptions: absent now and before; absent now but present before; present, symptoms new; present, symptoms worse or the same; or present, symptoms better. If an attack involved multiple areas on the body, designation of the defining symptom was based on the following hierarchy of anatomical involvement: laryngeal, gastrointestinal, facial, genitourinary, and extremity.

Patients could be discharged 60 minutes after treatment if deemed safe by the investigator. Patients who required a second dose of C1 INH-nf could be discharged 30 minutes after the second injection if clinically stable. Follow-up visits to assess for adverse events (AEs), changes in medical history, and blood sampling occurred 3 months after any injection of C1 INH-nf.

### Efficacy assessments

**Unequivocal relief** of the defining symptom was identified as at least 3 consecutive posttreatment reports of improvement at that site. Beginning of unequivocal relief was the time corresponding to the first of these 3 consecutive reports. Efficacy end points included the proportion of HAE attacks with unequivocal relief of the defining symptom within 1 and 4 hours after start of the first dose, time

to the beginning of unequivocal relief of the defining symptom, and proportion of patients who achieved unequivocal relief of the defining symptom within 4 hours after the start of treatment by attack number. A response proportion was calculated for each patient (number of attacks with unequivocal relief divided by the total number of attacks), and the mean of these response proportions was determined. Change in time to the beginning of unequivocal relief of the defining symptom for patients who received multiple treatments was evaluated, as were effects of treatment on C1 INH blood levels.

In the unequivocal relief analyses, patients who experienced substantial clinical relief but did not document 3 consecutive reports of unequivocal relief and patients for whom no posttreatment assessment was recorded were considered to have received failed treatment. To more accurately reflect real-world clinical practice, a second end point, *clinical relief*, was analyzed. Patients with either unequivocal relief or 1 or 2 consecutive assessments consistent with improvement followed by cessation of symptom assessments were included as responders in the clinical relief analyses.

Blood samples for complement testing (antigenic and functional C1 INH and C4) were collected before treatment and 60 minutes after C1 INH-nf administration at each short-term treatment visit.

### Safety assessments

Safety was evaluated by AEs and monitoring vital signs before and after treatment. Assays for markers of viral infection (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and parvovirus B19) were performed on blood samples collected before treatment at the first visit and 3 months after each dose (but not more frequently than every 3 months) for short-term treatment and preprocedural prophylaxis.

### Statistical analyses

Efficacy data were summarized and presented descriptively. Median time to the beginning of unequivocal relief and its 95% confidence interval were estimated by the Kaplan-Meier method. Changes in functional and antigenic C1 INH and C4 levels were evaluated before and after treatment; a paired *t* test was used to identify differences between pretreatment and posttreatment values. Summary statistics were prepared for all safety end points.

## Results

### Study population

From September 21, 2006, through March 31, 2009, 113 patients were enrolled in the study and received 1 or more doses of C1 INH-nf and are included in the intent-to-treat safety (ITT-S) population (Table 1). A total of 885 C1 INH-nf doses (median, 4.0 injections per patient; range, 1–114) were administered (800 for short-term treatment and 85 for preprocedural prophylaxis). The intent-to-treat efficacy (ITT-E) population included 101 patients who received C1 INH-nf for treatment of 1 or more attacks during the study. Demographics for the ITT-S population (Table 2) were similar for the ITT-E populations.

### Unequivocal relief

Among ITT-E patients, 609 attacks (range, 1–57 attacks per patient) were treated during the study and assessed for unequivocal relief. Fifteen patients received treatment for 10 attacks or more and 4 patients were treated for more than 20 attacks. The most common defining symptom was gastrointestinal edema (58.0%, 353/609). Extremity, laryngeal, facial, or genitourinary edema was the defining symptom reported in 14.1%, 13.8%, 11.8%, and 2.1% of attacks, respectively. Of the 84 laryngeal attacks, none required intubation after treatment with C1 INH-nf.

The proportion of attacks with unequivocal relief of the defining symptom was 68% within 1 hour after the start of treatment and

**Table 1**  
Patient disposition of the intent-to-treat safety population

| Disposition parameter                                                                     | No. (%) of patients <sup>a</sup> (N = 113) |
|-------------------------------------------------------------------------------------------|--------------------------------------------|
| Received C1 INH-nf for treatment of an acute attack (intent-to-treat efficacy population) | 101 (89.4)                                 |
| Received C1 INH-nf                                                                        |                                            |
| Received C1 INH-nf for short-term prophylaxis only                                        | 12 (10.6)                                  |
| Received C1 INH-nf for both short-term prophylaxis and an acute attack                    | 24 (21.2)                                  |
| Total                                                                                     | 36 (31.9)                                  |
| Completed study                                                                           | 43 (38.1)                                  |
| Did not complete study                                                                    | 70 (61.9)                                  |
| Reasons for not completing treatment                                                      |                                            |
| Transferred to open-label prophylaxis study with C1 INH-nf                                | 30 (26.5)                                  |
| 3-Month follow-up no longer required <sup>b</sup>                                         | 12 (10.6)                                  |
| Nonadherence to the protocol requirements                                                 | 9 (8.0)                                    |
| Transitioned to commercial C1 INH-nf                                                      | 6 (5.3)                                    |
| Lost to follow-up                                                                         | 6 (5.3)                                    |
| Consent withdrawn                                                                         | 6 (5.3)                                    |
| Death                                                                                     | 1 (0.9)                                    |

Abbreviation: C1 INH-nf, nanofiltered C1 esterase inhibitor (human).

<sup>a</sup>Denominator for percentages is the number of patients in the intent-to-treat safety population. Patients may have received C1 INH-nf as short-term prophylaxis before emergency or noncosmetic surgical or dental procedures and may not have received C1 INH-nf as treatment for an acute attack during the study. All patients who received any dose of C1 INH-nf are included in the intent-to-treat safety population.

<sup>b</sup>The requirement for a 3-month follow-up visit after the last treatment with C1 INH-nf was removed for the last 12 patients. This revision was made based on exposure of 259 patients to more than 12,000 doses of C1 INH-nf as treatment or prophylaxis without evidence of viral transmissions or serious adverse events causally related to the use of C1 INH-nf.

87% within 4 hours (Table 3). All genitourinary, 92% of extremity, 90% of gastrointestinal, 77% of laryngeal, and 75% of facial attacks achieved unequivocal relief within 4 hours after the start of the first dose of C1 INH-nf. The proportion of attacks achieving unequivocal relief was generally comparable across sex, race, and age. Attacks were classified with respect to time from attack onset until initiation of treatment. A higher proportion of attacks in patients treated 4 hours or less after onset achieved unequivocal relief within 1 hour after dosing compared with attacks treated more than 4 hours after onset (77% vs 56%). The proportion of attacks achieving unequivocal relief within 4 hours was not affected by time to initiation of treatment (89% vs 86%).

**Table 2**  
Demographics of the intent-to-treat safety population

| Demographic                              | No. (%) of patients <sup>a</sup> (N = 113) |
|------------------------------------------|--------------------------------------------|
| Age, y                                   |                                            |
| Mean (SD)                                | 34.5 (17.6)                                |
| Median                                   | 35.0                                       |
| Range                                    | 2–80                                       |
| Distribution of age, y                   |                                            |
| 2–5                                      | 1 (0.9)                                    |
| 6–11                                     | 10 (8.8)                                   |
| 12–17                                    | 13 (11.5)                                  |
| 18–64                                    | 81 (71.7)                                  |
| >64                                      | 8 (7.1)                                    |
| Sex                                      |                                            |
| Female                                   | 75 (66.4)                                  |
| Male                                     | 38 (33.6)                                  |
| Race                                     |                                            |
| White                                    | 91 (80.5)                                  |
| Black/African American                   | 9 (8.0)                                    |
| Hispanic/Latino                          | 5 (4.4)                                    |
| Asian                                    | 2 (1.8)                                    |
| American Indian or Alaska Native         | 5 (4.4)                                    |
| Other                                    | 1 (0.9)                                    |
| Patients taking danazol during the study | 26 (23.0)                                  |

<sup>a</sup>Data are presented as number (percentage) of patients unless otherwise indicated.

**Table 3**  
Unequivocal relief of the defining symptom within 1 and 4 hours after the start of the first dose of C1 INH-nf in the intent-to-treat efficacy population

| Defining symptom <sup>a</sup> | No. (%) of attacks with unequivocal relief |                |
|-------------------------------|--------------------------------------------|----------------|
|                               | Within 1 hour                              | Within 4 hours |
| Laryngeal <sup>b</sup>        | 50/84 (59.5)                               | 65/84 (77.4)   |
| Gastrointestinal              | 245/353 (69.4)                             | 318/353 (90.1) |
| Facial                        | 35/72 (48.6)                               | 54/72 (75.0)   |
| Genitourinary                 | 12/13 (92.3)                               | 13/13 (100)    |
| Extremity                     | 70/86 (81.4)                               | 79/86 (91.9)   |
| Not specified                 | 0/1                                        | 0/1            |
| All symptoms                  | 412/609 (67.7)                             | 529/609 (86.9) |

Abbreviation: C1 INH-nf, nanofiltered C1 esterase inhibitor (human).

<sup>a</sup>Listed by anatomical hierarchy.

<sup>b</sup>No laryngeal attack required intubation after C1 INH-nf infusion.

Of 101 patients treated for an attack during the study, 80 achieved unequivocal relief of the defining symptom of their first attack within 4 hours after the start of treatment (response rate, 79%). Median time to the beginning of unequivocal relief was 0.75 hour. The efficacy of C1 INH-nf for treatment of HAE attacks did not diminish with subsequent repeat administration (Table 4). For subsequent treated attacks, overall response rates and median time to relief were similar to those after treatment of the first attack. Two patients each had more than 32 attacks during the study; all but 2 of these attacks responded within 4 hours after C1 INH-nf dosing. Overall, the mean response proportion was independent of the number of attacks reported per patient.

Most attacks (69.1%) were treated successfully with 1 dose of C1 INH-nf; 30.9% received a second dose 60 minutes after the first. Analyses of patients with attacks requiring either 1 or 2 doses of C1 INH-nf found that the proportion of attacks achieving unequivocal relief of the defining symptom within 4 hours was comparable regardless of the number of doses. Attacks that required 1 dose of C1 INH-nf had a response rate of 89.5% (377/421 attacks in 83 patients) compared with 80.9% (152/188 attacks in 58 patients) for attacks that required 2 doses.

### Clinical relief

In the clinical relief analyses, 11 attacks without any posttreatment assessments were excluded; therefore, 598 attacks were included in

**Table 4**  
Unequivocal relief within 4 hours after the start of the first dose of C1 INH-nf and time to the beginning of unequivocal relief of the defining symptom by attack number in the intent-to-treat efficacy population

| Attack No. | No. of patients <sup>a</sup> | Patients with unequivocal relief, No. | Response rate (95% CI), % <sup>b</sup> | Median time to beginning of unequivocal relief (95% CI), h |
|------------|------------------------------|---------------------------------------|----------------------------------------|------------------------------------------------------------|
| 1          | 101                          | 80                                    | 79 (70–87)                             | 0.75 (0.50–1.00)                                           |
| 2          | 77                           | 64                                    | 83 (73–91)                             | 0.75 (0.50–1.25)                                           |
| 3          | 58                           | 52                                    | 90 (79–96)                             | 0.50 (0.50–0.75)                                           |
| 4          | 50                           | 43                                    | 86 (73–94)                             | 0.75 (0.50–1.00)                                           |
| 5          | 38                           | 32                                    | 84 (69–94)                             | 0.75 (0.50–1.25)                                           |
| 6          | 29                           | 23                                    | 79 (60–92)                             | 0.50 (0.25–0.75)                                           |
| 7          | 23                           | 21                                    | 91 (72–99)                             | 0.75 (0.50–0.75)                                           |
| 8          | 20                           | 19                                    | 95 (75–100)                            | 0.50 (0.25–0.75)                                           |
| 9          | 18                           | 16                                    | 89 (65–99)                             | 0.25 (0.25, 0.50)                                          |
| 10         | 15                           | 12                                    | 80 (52–96)                             | 0.50 (0.25, 0.75)                                          |
| 15         | 9                            | 8                                     | 89 (52–100)                            | 0.50 (0.50, 1.00)                                          |
| 20         | 6                            | 6                                     | 100 (54–100)                           | 0.25 (0.25, 0.75)                                          |
| 25         | 4                            | 4                                     | 100 (40–100)                           | 0.25 (0.25, 1.75)                                          |
| 30         | 3                            | 3                                     | 100 (29–100)                           | 0.25 (0.25, 1.75)                                          |

Abbreviations: C1 INH-nf, nanofiltered C1 esterase inhibitor (human); CI, confidence interval; HAE, hereditary angioedema.

<sup>a</sup>Number of patients with the corresponding number of HAE attacks. For example, 101 patients experienced at least 1 HAE attack during the study and 77 had at least 2 HAE attacks.

<sup>b</sup>Response rate is the proportion of patients with unequivocal relief of the defining symptom within 4 hours.

**Table 5**

Clinical relief of the defining symptom within 1 and 4 hours after the start of the first dose of C1 INH-nf

| Defining symptom <sup>a</sup> | No. (%) of attacks with clinical relief |                |
|-------------------------------|-----------------------------------------|----------------|
|                               | Within 1 hour                           | Within 4 hours |
| Laryngeal <sup>b</sup>        | 51/78 (65.4)                            | 70/78 (89.7)   |
| Gastrointestinal              | 260/351 (74.1)                          | 339/351 (96.6) |
| Facial                        | 41/70 (58.6)                            | 64/70 (91.4)   |
| Genitourinary                 | 12/13 (92.3)                            | 13/13 (100)    |
| Extremity                     | 72/86 (83.7)                            | 85/86 (98.8)   |
| All symptoms                  | 436/598 (72.9)                          | 571/598 (95.5) |

Abbreviation: C1 INH-nf, nanofiltered C1 esterase inhibitor (human).

<sup>a</sup>Listed by anatomical hierarchy.

<sup>b</sup>No laryngeal attack required intubation after C1 INH-nf infusion.

these analyses. The proportion of HAE attacks with clinical relief of the defining symptom was 72.9% within 1 hour and 95.5% within 4 hours (Table 5). All genitourinary, 99% of extremity, 97% of gastrointestinal, 91% of facial, and 90% of laryngeal attacks achieved clinical relief of the defining symptom within 4 hours. A greater proportion of attacks treated within 4 hours of onset achieved clinical relief within 1 hour vs when treatment was delayed beyond 4 hours (81% vs 60%). In patients with 10 attacks or more, the clinical relief response rate within 4 hours after the start of treatment ranged from 79% to 100%, comparable to the unequivocal relief response rate.

#### Pharmacokinetics

Administration of C1 INH-nf generally resulted in increases in serum levels of antigenic and functional C1 INH activity within 1 hour of administration. Median increases in C1 INH antigen values were slightly lower in patients 18 years or older than in patients younger than 18 years (Fig 1). The mean percentage increase in functional C1 INH activity from before to after treatment was approximately 21% to 66% in patients 18 years or older and 20% to 88% in patients younger than 18 years. The mean increases in functional C1 INH activity from before to after treatment were generally similar for varying numbers of attacks. The C4 values 60 minutes after treatment did not change significantly compared with preinjection values and did not differ between the age groups.

#### Safety results

Treatment-emergent adverse events (TEAEs) were reported by 46 of 113 patients (41%) (Table 6). Of the 129 TEAEs, most (87%, 112) were of mild or moderate intensity. Three patients reported 4

**Table 6**

Treatment-emergent adverse events reported in 2% of patients or more in the intent-to-treat safety population

| Adverse event             | No. (%) of patients (N=113) |
|---------------------------|-----------------------------|
| Sinusitis                 | 6 (5.3)                     |
| Nasopharyngitis           | 5 (4.4)                     |
| Pharyngitis streptococcal | 4 (3.5)                     |
| Hereditary angioedema     | 4 (3.5)                     |
| Bronchitis                | 3 (2.7)                     |
| Constipation              | 3 (2.7)                     |
| Cough                     | 3 (2.7)                     |
| Rash                      | 3 (2.7)                     |

TEAEs considered related to C1 INH-nf. Of these, 2 events were possibly related (injection site pain and rash) and 2 (sinusitis and joint swelling) were of unknown relationship to C1 INH-nf. No patients discontinued use of the study drug because of an AE.

Thirteen serious TEAEs were experienced by 6 patients (5%); however, all serious TEAEs were considered unrelated to the study drug. One death reported during the study resulted from chemotherapy-resistant B-cell lymphoma, which was not considered related to C1 INH-nf. There was no evidence of human immunodeficiency virus or viral hepatitis transmission or detection of clinically relevant anti-C1 INH antibodies.

#### Discussion

This open-label, single-arm, multicenter study evaluated the efficacy and safety of repeat use of C1 INH-nf, 1,000 U IV, for the treatment of 609 HAE attacks. This study represents one of the largest data sets and prospective evaluations of C1 INH therapy for HAE attacks. It provided patients with expanded and compassionate use access to C1 INH-nf for the treatment of HAE attacks because no C1 INH product was commercially available in the United States at that time. In the previous randomized short-term treatment trial with C1 INH-nf, 1,000 U, the median time to onset of unequivocal relief was 2 hours in patients in the C1 INH-nf group but more than 4 hours in those administered placebo ( $P = .02$ ).<sup>11</sup> In the current study, C1 INH-nf was effective in treating most attacks, with 87% achieving unequivocal relief within 4 hours. Moreover, within 4 hours, 95.5% achieved clinical relief, an end point that more closely reflects clinical practice. By either analysis, C1 INH-nf showed efficacy in treating most HAE attacks. The efficacy of C1 INH-nf did not diminish with subsequent repeat administration; the number of attacks reported during the study appeared to have no effect on achievement of unequivocal or clinical relief.

Upper airway obstruction can be life-threatening when laryngeal angioedema occurs in HAE patients.<sup>6</sup> Patients presenting with laryngeal angioedema were not eligible for the previous placebo-controlled trial<sup>11</sup>; however, in this study, 84 laryngeal attacks were treated with C1 INH-nf. Most laryngeal attacks achieved relief of the defining symptom within 4 hours after the start of treatment, and more importantly, no patient required intubation after receiving C1 INH-nf.

Both the unequivocal and clinical relief analyses demonstrated that earlier treatment with C1 INH-nf resulted in earlier relief of symptoms, which is consistent with previous reports.<sup>12,13</sup> A higher proportion of attacks treated 4 hours or less after onset achieved clinical relief within 1 hour after dosing compared with attacks treated more than 4 hours after onset (81.3% vs 59.8%). In addition, and perhaps as a consequence of 1-hour response rates, a lower percentage of patients treated 4 hours or less after symptom onset received a second dose of C1 INH-nf compared with patients treated more than 4 hours into the attack (21.2% vs 44.4%). This difference in response rates associated with time to treatment was absent by the 4-hour time point when 95.6% of 4-hour or less and 95.3% of more than 4-hour time-to-treatment groups achieved

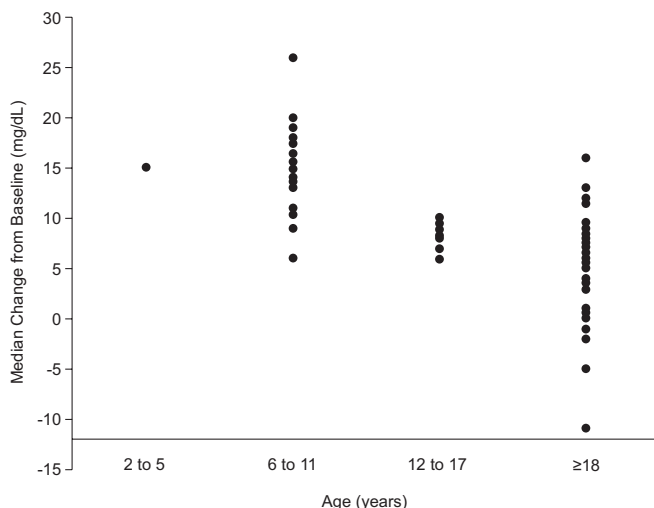


**Figure 1.** Summary of median change in C1 inhibitor (C1 INH) antigen values from before treatment to 1 hour after treatment, by age.

clinical relief. This finding may be partially attributable to the increased number of second doses given in the latter group. These study observations underscore the importance of prompt treatment with C1 INH to reduce symptom duration and associated morbidity, as well as possibly reducing the dose of C1 INH required to achieve clinical symptom relief, thereby potentially reducing treatment costs. Early treatment may be particularly important when treating laryngeal attacks in which delayed clinical response could result in airway complications and/or intubation.

In this study, a 1,000-U dose of C1 INH-nf was administered, which is consistent with the standard of care in Europe, where C1 INH therapy has been used to treat HAE attacks for more than 30 years.<sup>14,15</sup> A recent double-blind, placebo-controlled study found that 20 U/kg of a pasteurized C1 INH product was statistically superior to placebo for median time to onset of symptom relief in abdominal or facial attacks in HAE patients, whereas 10 U/kg was not statistically superior.<sup>8</sup> This finding suggests that higher doses of C1 INH for HAE attacks may be clinically beneficial in some cases. Nevertheless, 19% of patients who received the higher dose required rescue medication after 4 hours because of insufficient or no symptom relief. In this study, which included patients experiencing HAE attacks involving various sites of the body, including laryngeal, approximately 30% of HAE attacks were treated with a second dose of C1 INH-nf. How C1 INH dosing may have affected the measured outcomes of this study is unclear given the clinical variability and unpredictability of HAE attacks in terms of speed of symptom progression, location(s) of edema, and severity. Historically, C1 INH therapy provides a response rate of approximately 95% for HAE attacks.<sup>7,9,12</sup> Although comparisons among studies of C1 INH products are difficult because trial designs have differed, and one limitation of this study is its open-label design, results reported herein are consistent with previous reports of C1 INH therapy. Recent double-blind and open-label short-term treatment studies with 2 plasma-derived C1 INH products available in the United States have shown similar results despite differences in dosing and outcome measure methods. Double-blind and open-label studies with pasteurized C1 INH dosed at 20 U/kg (1,500 U for a 75-kg patient) demonstrated median time to onset of symptom relief of 0.5 and 0.46 hour, respectively.<sup>8,16</sup> For C1 INH-nf dosed at 1,000 U, a previous double-blind study and the open-label data presented herein demonstrated median time to unequivocal symptom relief of 2 and 0.75 hour, respectively.<sup>11</sup> Whether the observed variability is attributable to dosing, outcome measure methods, study design, or other factors is unknown.

Ecallantide, a plasma kallikrein inhibitor, and icatibant, a selective bradykinin B<sub>2</sub>-receptor antagonist, have also shown benefit in the treatment of HAE attacks in placebo-controlled studies.<sup>17–19</sup> Ecallantide provided significantly greater improvement in symptoms 4 hours after dosing compared with placebo.<sup>17,19</sup> Time to improvement of symptoms was approximately 2 hours with ecallantide compared with more than 4 hours with placebo.<sup>17</sup> In 2 controlled studies, treatment with icatibant showed a time to clinically significant relief of 2.0 to 2.5 hours vs 4.6 to 12.0 hours in the control arms.<sup>18</sup> Although it is impossible to directly compare results across all recent HAE treatment studies because of differences in methods and efficacy measures, treatment effects for C1 INH, ecallantide, and icatibant appear similar. Subsequently, short-term treatment options have been incorporated into recent HAE consensus documents on the management of HAE.<sup>20</sup>

Although not typically followed in clinical practice, functional C1 INH activity increased by 20% to 88% within 1 hour of C1 INH-nf administration in this study. Posttreatment C4 values were similar to baseline levels, which was not unexpected because exogenously administered C1 INH does not directly increase C4 as it does C1 INH but instead lowers the metabolism of C4.<sup>4</sup> An increase in C4 levels typically is not seen until 24 to 48 hours after injection.

Repeat administration of C1 INH-nf was safe and well tolerated. There was no evidence of viral transmission associated with C1 INH-nf administration, and nanofiltration provides an additional level of safety against enveloped and nonenveloped viruses and possibly prions.<sup>11,21</sup> In conclusion, the results of this open-label study support the efficacy and safety of C1 INH-nf for short-term treatment of HAE attacks.

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