

Escalating Doses of C1 Esterase Inhibitor (CINRYZE) for Prophylaxis in Patients With Hereditary Angioedema

Jonathan A. Bernstein, MD^a, Michael E. Manning, MD^b, Henry Li, MD, PhD^c, Martha V. White, MD^d, James Baker, MD^e, William R. Lumry, MD^f, Mark A. Davis-Lorton, MD^g, Kraig W. Jacobson, MD^h, Richard G. Gower, MDⁱ, Colin Broom, MD^j, David Fitts, PhD, MPHⁱ, and Jennifer Schranz, MD^j Cincinnati, Ohio; Scottsdale, Ariz; Chevy Chase and Wheaton, Md; Lake Oswego and Eugene, Ore; Dallas, Tex; Mineola, NY; Spokane, Wash; and Exton, Pa

What is already known about this topic? Nanofiltered C1 inhibitor (human) (1000 U every 3 or 4 days) is well tolerated and effective in preventing angioedema attacks in most patients with hereditary angioedema. Variability of disease may require individualized dosing. Tolerability, including thrombogenicity, has not been evaluated at higher doses.

What does this article add to our knowledge? Dose escalation of C1 INH-nf from 1000 U up to 2500 U every 3-4 days for 12 weeks was well tolerated. No systemic thrombotic events occurred in this study of 20 patients.

How does this study impact current management guidelines? These data are encouraging and may guide clinicians' management strategies for patients with hereditary angioedema who are not adequately controlled on the approved dose of 1000 U every 3 or 4 days.

BACKGROUND: Nanofiltered C1 inhibitor (human) is approved in the United States for routine prophylaxis of angioedema attacks in patients with hereditary angioedema, a rare disease caused by a deficiency of functional C1 inhibitor. **OBJECTIVE:** To assess the safety of escalating doses of nanofiltered C1 inhibitor (human) in patients who were not

adequately controlled on the indicated dose (1000 U every 3 or 4 days).

METHODS: Eligible patients had >1 attack/month over the 3 months before the trial. Doses were escalated to 1500 U every 3 or 4 days for 12 weeks, at which point, the patients were evaluated. If treatment was successful (≤ 1 attack/mo) or at the

^aDivision of Immunology, Allergy, and Rheumatology, and Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio

^bAllergy, Asthma and Immunology Associates, Ltd, Scottsdale, Ariz

^cInstitute for Asthma and Allergy, Chevy Chase, Md

^dInstitute for Asthma and Allergy, Wheaton, Md

^eAllergy Asthma & Dermatology Associates, Lake Oswego, Ore

^fAARA Research Center, Dallas, Tex

^gDivision of Rheumatology and Immunology, Winthrop University Hospital, Mineola, NY

^hAllergy and Asthma Research Group, Eugene, Ore

ⁱMarycliff Allergy Specialists, Spokane, Wash

^jClinical Research for Broom and Schranz and Biostatistics for Fitts, ViroPharma Incorporated, Exton, Pa

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Corresponding author: Jonathan A. Bernstein, MD, Division of Immunology (M1563), University of Cincinnati, 3255 Eden Ave ML#563, Suite 350, Cincinnati, OH 45267-0563. E-mail: Jonathan.Bernstein@uc.edu. 2213-2198/\$36.00

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*Abbreviations used**C1 INH- C1 Esterase inhibitor**C1 INH-nf- Nanofiltered C1 INH (human)**HAE- Hereditary angioedema*

investigator's discretion, the patients entered a 3-month follow-up period. The patients with an average of >1 attack/month were eligible for further escalation to 2000 U and then 2500 U.

RESULTS: Twenty patients started at 1500 U; 13 were escalated to 2000 U, and 12 were escalated to 2500 U. Eighteen patients reported adverse events. Two patients reported 4 serious adverse events (cerebral cystic hygroma, laryngeal angioedema attack, anemia, and bile duct stone) that were considered by investigators to be unrelated to treatment. Notably, there were no systemic thrombotic events or discontinuations due to adverse events. Fourteen patients were treated successfully (70%), continued to the follow-up period at the investigator's discretion, or experienced a reduction in attacks of >1.0/month.

CONCLUSIONS: Dose escalation of nanofiltered C1 inhibitor (human) up to 2500 U was well tolerated and reduced attack frequency in the majority of patients. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:77-84)

Key words: Hereditary angioedema; HAE; Angioedema; C1 esterase inhibitor; C1 INH; Dose escalation; Thrombotic events; Prophylaxis; Treatment

Hereditary angioedema (HAE) is a rare autosomal dominant disorder that occurs in 1 in 10,000-50,000 people and is caused by a deficiency of functional C1 esterase inhibitor (C1 INH).^{1,2} In the United States, nanofiltered C1 INH (human) (C1 INH-nf) (CINRYZE; ViroPharma) is indicated for routine prophylaxis against angioedema attacks in adolescents and adults with HAE.³ In Europe, C1 INH-nf is approved for the acute treatment and preprocedural prevention of angioedema attacks and for the routine prevention of angioedema attacks in adults and adolescents with HAE who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.⁴ The approved dose for prophylaxis of angioedema attacks is 1000 U administered intravenously every 3 or 4 days. Previous studies^{5,6} showed that most patients experienced reductions in the frequency, severity, and duration of angioedema attacks while receiving this dose of C1 INH-nf; however, a few patients' attacks were not adequately controlled on the indicated dose. This open-label, multicenter, phase 4 study was conducted to assess the safety, tolerability, immunogenicity, and clinical effect of escalating doses of C1 INH-nf doses as prophylactic therapy for angioedema attacks in patients who were not adequately controlled while receiving 1000 U every 3 or 4 days. The study was mandated by the US Food and Drug Administration as a contingency for approval of the product in October 2008.

METHODS

Patients

The study was conducted between August 2009 and May 2012. Patients were eligible for the study if they were ≥6 years of

age, weighed ≥25 kg, had a confirmed diagnosis of HAE, and had an average of >1.0 attack/month, regardless of severity, in the 3 months before the study, while receiving 1000 U C1 INH every 3 or 4 days. An HAE diagnosis was defined as a documented history of swelling in the face, extremities, gastrointestinal tract, genitalia, or larynx, in addition to at least one of the following criteria: C1 INH gene mutation; C4, C1 inhibitor antigen, or functional C1 inhibitor below the lower limit of the reference range; or a family history of HAE.

Patients were excluded from the study if they had a surgical or medical condition that could have interfered with administration of the study medication or interpretation of the study results, had a history of abnormal blood clotting, used prescription anticoagulant medication, had a history of an allergic reaction to C1 INH-nf or similar products, had participated in any other investigational drug study within the 30 days before study entry, or were pregnant or breastfeeding. Patients also were excluded if they had hemoglobin, white blood cell count, platelet count, or serum aspartate aminotransferase and/or alanine aminotransferase laboratory values outside the normal range at screening.

Study design

A treatment algorithm was used to escalate doses of C1 INH-nf at 500-U intervals (1500, 2000, and 2500 U) for successive 12-week treatment periods. At the end of each treatment period, the patients were evaluated for tolerability and attack frequency. Attacks of any severity and location were counted. The patients who tolerated their current dose and had an average of ≤1 attack/month continued to receive their current dose for a 3-month follow-up period and then completed the study. Consistent with actual clinical practice, investigators also applied clinical judgment to determine whether patients showed sufficient improvement to continue at the current dose. When making this decision, the investigators took into account the full clinical picture, including the number, severity, location, and historic rate of attacks. Thus, even if the overall attack rate was >1 attack/month, the investigator could have concluded that the patient tolerated the current dose and showed sufficient improvement from the historic attack rate. These patients also entered the 3-month follow-up period at the current dose and then completed the study. Otherwise, patients with an average of >1 attack/month received dose escalation to the next dose level and received infusions every 3 or 4 days for 12 weeks. Patients who completed the 2500-U dosing step but did not proceed to follow-up completed the study.

The first and last doses of each escalation step and the last dose of the follow-up period were administered by study personnel at the investigational site. All other doses of the study drug were administered by study personnel at the investigational site or by trained health care personnel at the patient's home or workplace. Concomitant medications taken from day 1 and continuing until the end of therapy with the study drug were recorded throughout the study. There were no prohibited medications. Patients and caregivers used a study diary to document daily information about any attacks that occurred. Attacks included any swelling or pain typical of an angioedema attack. Investigators monitored compliance, tolerability, and adverse events.

This study was performed according to the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice.

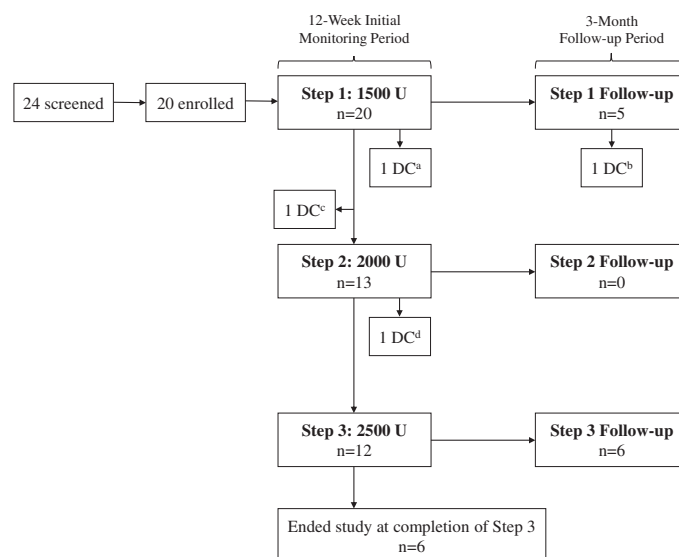


FIGURE 1. Patient disposition. ^aThe patient discontinued treatment (day 28) due to withdrawal of consent after receiving a total of 9 doses. ^bThe patient discontinued treatment (day 162) at investigator or sponsor discretion: the patient missed the last dose of the follow-up period and, therefore, was considered to have discontinued from the study. ^cThe patient discontinued treatment (day 83) at investigator or sponsor discretion after receiving a total of 24 doses. ^dPatient discontinued treatment (day 113) due to withdrawal of consent after receiving a total of 33 doses (Step 1: 24 doses; Step 2: 9 doses). DC, Discontinuation.

Before the initiation of any study procedures, the investigators obtained written informed consent from each patient or guardian.

Assessments

The primary end point of this study was safety, which was evaluated by monitoring adverse events, vital signs, and clinical laboratory test results. Blood samples obtained at baseline, the end of each dosing step, and the end of follow-up were evaluated for the presence of antibodies to C1 INH by Sanquin Diagnostic Services. Thrombotic events were of particular interest, and the investigators and patients were given instructions on how to recognize the signs and symptoms of a thrombotic event. Guidance was provided on both diagnostic and treatment algorithms, including the assessment of risk factors for thrombosis, and investigators were instructed to report thrombotic events as serious adverse events. The number of angioedema attacks were tallied from patients' diaries. Symptoms of angioedema that occurred on consecutive days were considered to be part of a single attack. For each treatment period, the number of attacks was normalized for the duration of that period and expressed as a monthly attack rate.

Patients who reported an average monthly attack rate of ≤ 1.0 at the end of any step (week 12) were categorized as per-protocol treatment successes. Patients with a monthly attack rate of >1.0 but whom the investigator deemed were stable enough to continue to the follow-up period at the current dose, were categorized as investigator-determined treatment successes. A *post hoc* analysis also identified patients whose historic attack rates were reduced by more than 1.0 at the end of any step, which indicated a decreased disease burden. Patients who experienced an average monthly attack rate >1.0 , did not continue to follow-up, and did not experience a reduction in monthly attack rate from a historic attack rate of >1.0 were categorized as having treatment failures.

RESULTS

Patient disposition

Of the 24 patients who were screened for this study, 20 were enrolled and received 1500 U in the first dosage step, 13 of these patients escalated to 2000 U, and 12 of these patients escalated to 2500 U. Overall, 4 patients discontinued the study; 2 patients withdrew consent and 2 patients discontinued at investigator and/or sponsor discretion (Figure 1).

Baseline demographics

Fourteen of the 20 patients (70%) were female patients, and 18 (90%) were white (Table I). At baseline, the mean age was 41.7 years (range, 16-77 years). During the year before study enrollment, patients reported a mean of 4.4 attacks/month, with the majority of attacks (95%) occurring in the abdomen or the extremities. Patients reported a mean of 1.7 hospital visits for angioedema attacks during the year before enrollment.

Safety

The primary objective of this study was to assess the safety of escalating doses of C1 INH-nf. Overall, C1 INH-nf was well tolerated at all dose levels. The majority of adverse events were considered by the investigator to be unrelated to the study drug (86/91 [95%]) and were mild to moderate in intensity (77/91 [85%]). Eighteen patients (90%) experienced ≥ 1 adverse event. The most frequently reported adverse events were upper respiratory tract infection (5 [25%]) and nasopharyngitis (3 [15%]) (Table II). No patients discontinued study medication because of an adverse event.

Two patients (10%) reported adverse events that were considered by the investigator to be related to the study drug. One patient developed a medical device complication (verbatim: blood clot in port) during the first dosage step; the clot resolved completely with streptokinase. Based on a review of medical history and adverse event information, 3 other patients reported

TABLE I. Baseline demographics and characteristics

Parameter	C1 INH-nf (N = 20)
Age (y)	
Mean (SD)	41.7 ± 15.3
Median (range)	41.5 (16-77)
Distribution of age, no. (%)	
12-17 y	1 (5)
18-44 y	12 (60)
45-64 y	6 (30)
>75 y	1 (5)
Female patients, no. (%)	14 (70)
Female BMI (kg/m ²)	
Mean (SD)	30.2 ± 6.7
Median (range)	30.1 (21-42)
Male BMI (kg/m ²)	
Mean (SD)	33.1 ± 5.5
Median (range)	33.8 (25-40)
Race, no. (%)	
White	18 (90)
Black or African American	1 (5)
Other*	1 (5)
Average no. of angioedema attacks per month during the year before enrollment	
Mean (SD)	4.4 ± 3.1
Median (range)	3.0 (2-11)
Distribution of the average no. monthly attacks during the year before enrollment	
1-3 attacks/mo	10 (50)
>3 attacks/mo	10 (50)
No. (%) of patients who experienced at least 1 attack in each anatomic region in the year before enrollment†	
Abdominal	19 (95)
Extremity	19 (95)
Genitourinary	12 (60)
Facial	10 (50)
Laryngeal	9 (45)
Other‡	7 (35)
No. of hospital visits necessary for angioedema attacks during the year before enrollment	
Mean (SD)	1.7 ± 3.3
Median (range)	0 (0-10)
Distribution of hospital visits during the year before enrollment, no. (%)	
0	14 (70)
1-5	3 (15)
6-10	3 (15)
Distribution of the average no. of days of missed work and/or school during the year before enrollment, no. (%)	
0	7 (35)
1-2	6 (30)
3-5	2 (10)
6-10	2 (10)
>10	3 (15)

BMI, Body mass index.

*Race was recorded as Mexican.

†A patient may have had more than 1 attack location during the prior year.

‡Included back (upper and lower), neck, and chest.

the presence of catheter ports without having any complications. The patient with the clot in the port also experienced catheter-site pain on the first days of the first and third dosing steps and dyspnea in the third dosage step. The dyspnea occurred on the first day of the 2500-U treatment period (the time of the event was not recorded relative to the timing of dosing) and most likely was an infusion-related event. The event was mild, resolved without medication, and did not lead to discontinuation of study medication. A second patient experienced muscle spasms during the second dosage step.

Two patients experienced serious adverse events. One patient was diagnosed with a cerebral cystic hygroma during the third dosage step. A second patient experienced a laryngeal angioedema attack during the first dosage step, and anemia and cholelithiasis during the second dosage step that required hospitalization. No serious adverse events were determined by the investigator to be related to the study drug. No systemic thrombotic events occurred.

Antibodies to C1 INH were detected in 2 patients. One patient had antibodies before the first dose that were detectable through each dose escalation step, and 1 patient first had borderline detectable antibodies at the end of the third dosage step (2500 U). Neither patient reported a family history of HAE, and both patients (ages 56 and 59 years) were diagnosed late in life (<2 years since diagnosis). The first patient was evaluated before the study for a diagnosis of acquired angioedema with specific laboratory testing, including a bone marrow examination, and all tests results were unremarkable. After the study, with repeated laboratory testing, this patient had been diagnosed as having monoclonal gammopathy of unknown significance, and the diagnosis of acquired angioedema was confirmed. The second patient was suspected to have acquired angioedema.

Functional C1 inhibitor levels

Functional C1 inhibitor levels for each patient at baseline and each dosage step, including follow-up, if applicable, are shown in Table E1 (in this article's Online Repository at www.jaci-inpractice.org).

Treatment effect

The secondary objective of this study was to evaluate the effect of escalating doses of C1 INH-nf on the monthly rate of angioedema attacks. The results of treatment status (the categorization of each patient's treatment as per-protocol success, investigator-determined success, reduction >1.0/mo, or failure) for each dosage step are shown in Table III. Four patients were per-protocol successes while receiving 1500 U for 12 weeks, and 1 patient was an investigator-determined success. Four of these 5 patients continued to receive 1500 U during the 3-month follow-up period: 1 of these discontinued treatment during the follow-up period (Figure 1). Of the remaining 15 patients, 2 discontinued treatment before proceeding to dose escalation at step 2. One of these patients had a reduction in attack rate of >1.0 attack/month during the 1500-U treatment period and discontinued at the end of the treatment period because he was traveling out of the country. Another patient withdrew consent during the 1500-U treatment period and was considered to have had a treatment failure.

The remaining 13 patients were escalated to 2000 U. One of these patients discontinued treatment during step 2 (moved out of state) and was considered to have had a treatment failure. Aside from the patient who discontinued during step 2, no patients who entered step 2 met the criteria for treatment success

TABLE II. Exposure and adverse events

	C1 INH-nf dosage step			All patients (N = 20)
	1500 U (n = 20)	2000 U (n = 13)	2500 U (n = 12)	
Exposure duration (d)*				
Mean (SD)	101 ± 42.2	78 ± 15.2	124 ± 43.5	229 ± 93.1
Median (range)	82 (28-180)	82 (28-85)	124 (81-166)	250 (28-341)
Patients with ≥1 adverse event, no. (%)				
All	15 (75)	11 (85)	11 (92)	18 (90)
Related to the study drug	1 (5)	1 (8)	1 (8)	2 (10)
Adverse events reported in ≥1 patient, no. (%)				
Upper respiratory tract infection	3 (15)	4 (31)	3 (25)	5 (25)
Nasopharyngitis	3 (15)	0	0	3 (15)
Abdominal discomfort	1 (5)	0	1 (8)	2 (10)
Arthralgia	1 (5)	0	1 (8)	2 (10)
Diarrhea	2 (10)	0	0	2 (10)
Ligament sprain	1 (5)	1 (8)	1 (8)	2 (10)
Medical device complication	2 (10)	0	0	2 (10)
Edema peripheral	2 (10)	0	0	2 (10)
Pain in extremity	1 (5)	1 (8)	1 (8)	2 (10)
Rhinitis	0	1 (8)	1 (8)	2 (10)
Sinusitis	1 (5)	0	1 (8)	2 (10)
Urinary tract infection	1 (5)	0	2 (17)	2 (10)
Patients with serious adverse events, no. (%)				
All	1 (5)	1 (8)	1 (8)	2 (10)
Related to the study drug	0	0	0	0
Patients who discontinued from study due to adverse events				
	0	0	0	0

*For each subject, exposure duration is defined as date of last dose minus date of first dose (at given step) plus 1 day. For the “All patients” column, exposure duration is defined as date of last dose minus date of first dose (Step 1) in study plus 1 day.

TABLE III. Treatment status of patients who received escalating doses of C1 INH-nf

Treatment status	C1 INH-nf dosage step			Total (N = 20)	Cumulative total (N = 20)
	1500 U (n = 20)	2000 U (n = 13)	2500 U (n = 12)		
Per-protocol success, no. (%) (average monthly angioedema attack rate <1.0 at the end of any step and continued to follow-up)	4 (20)	0	5 (42)	9 (45)	9 (45)
Investigator-determined success, no. (%) (continued to follow-up period based on investigator’s clinical judgment)	1 (5)	0	1 (8)	2 (10)	11 (55)
Reduction >1.0, no. (%) (reduction from historic attack rate of >1 at the end of any step)	1 (5)	0	2 (17)	3 (15)	14 (70)
Failure, no. (%) (average monthly attack rate >1.0, did not continue to follow-up, and did not have a reduction from historical attack rate >1.0)	1 (5)*	1 (8)*	4 (33)	6 (30)	NA

NA, Not applicable.

*Discontinuation at this step.

at the end of the step 2 treatment period. Therefore, in accordance with the protocol, they received a dose escalation to 2500 U. After 12 weeks of treatment at 2500 U, 5 patients had per-protocol successes, and 1 patient had an investigator-determined success. All 6 of these patients continued to receive 2500 U during the 3-month follow-up period. Of the patients who did not enter the follow-up period, 2 had a reduction of >1.0 attack/month during the 2500-U treatment period, and 4 were considered to have had treatment failures during this period.

Overall, 9 patients (45%) met criteria for per-protocol treatment success, 2 (10%) were investigator-determined successes,

and 3 additional patients (15%) experienced a reduction of >1.0 attack/month. Attack rates for each patient at each dosage step are displayed in Figure 2. Overall, the majority of patients (14 [70%]) experienced notably reduced rates (per protocol, investigator determined, and reduction >1.0) of angioedema attacks in comparison with the historic attack rate while receiving escalated doses of C1 INH-nf. Patients who proceeded to the 3-month follow-up period (11 [55%]) at their final dose continued to experience similarly low attack rates (see Figure E1 in this article’s Online Repository at www.jaci-inpractice.org).

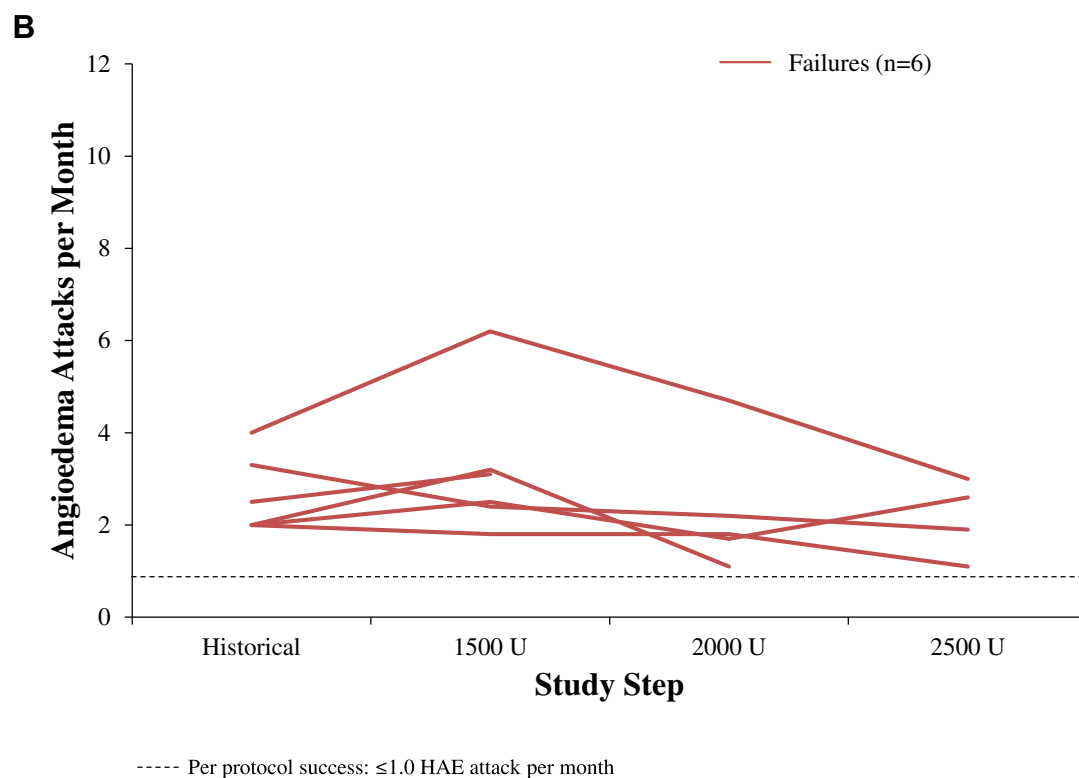
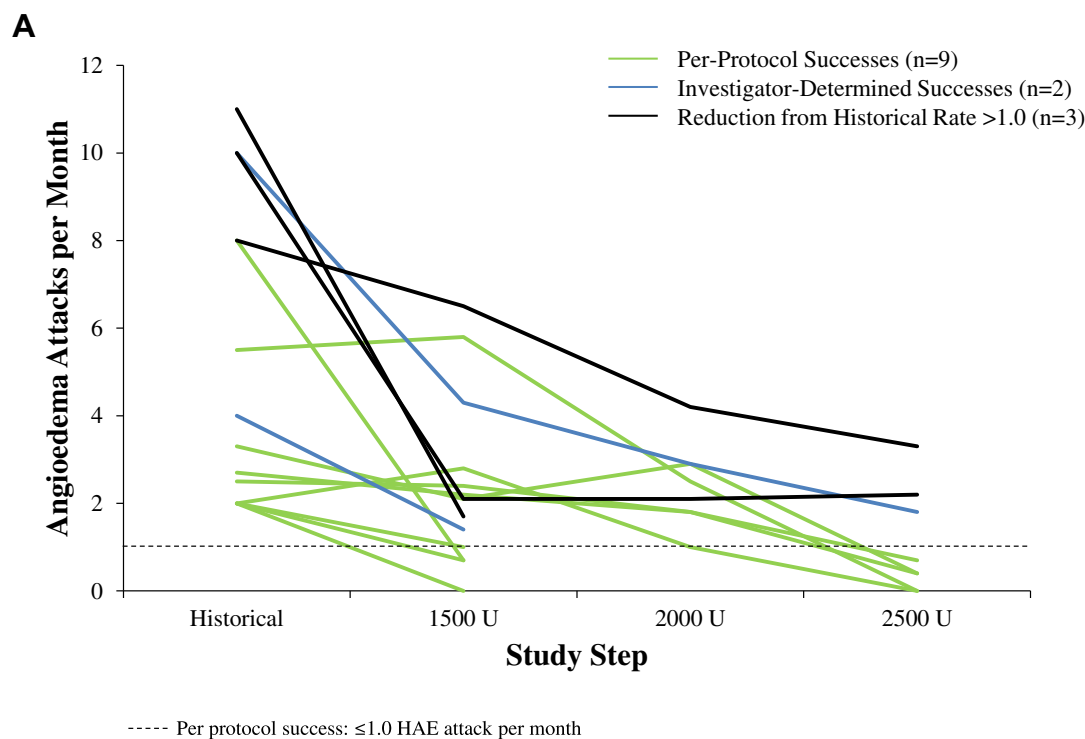


FIGURE 2. The monthly attack rate at each dosage step. **A**, Per-protocol successes, investigator-determined successes, and reduction from historic rate >1.0. **B**, Failures.

Six patients (30%) were categorized as having treatment failures. One of these patients experienced a reduction of 1.4 attacks/month by the end of the 2500-U dosing step. However, this patient was considered to have had a treatment failure because the majority of attacks were severe, including some with laryngeal involvement. Two of the patients considered as having treatment failures were those described above who had antibodies to C1 INH at one or more time points during the study. Neither patient reported a family history of HAE, and both patients were diagnosed late in life (<2 years since diagnosis).

The need for dose escalation did not appear to be related to weight, age, age at diagnosis of HAE, history of laryngeal attacks in the past year, or baseline C1 INH/C4 levels (data not shown). The following numbers of patients reported androgen use during the study: 1 of 9 per-protocol successes; 1 of 2 investigator-determined successes; 2 of 3 patients with a monthly attack reduction >1.0; and 2 of 6 who had had treatment failures.

DISCUSSION

As a contingency for approval, the US Food and Drug Administration asked the sponsor to conduct a study that evaluated the safety and treatment effect of C1 INH-nf doses higher than 1000 U in patients who were not adequately controlled on the 1000 U dose. The study required almost 3 years to enroll 20 eligible patients, which suggests that these patients were uncommon. In a previously conducted open-label study of 1000 U C1 INH-nf every 3 or 4 days for the routine prophylaxis of angioedema attacks,⁶ the patients showed a 94% reduction in monthly attack rate from a median historic rate of 3 attacks/month to a rate of 0.19 attacks/month. Four of 146 patients (2.7%) who were receiving 1000 U twice weekly in this study⁶ would have met these entry criteria for the present dose escalation study, which indicates that the majority of patients were adequately controlled on the approved dosage.

The results of our study indicated that the safety profile of C1 INH-nf doses up to 2500 U every 3 or 4 days for 6 months is consistent with the known safety profile at the approved 1000-U regimen. Most adverse events were mild or moderate in intensity and were not serious. No patients discontinued C1 INH-nf treatment because of an adverse event. Although 2 patients reported serious adverse events, none of the events were considered by the investigator to be related to C1 INH-nf treatment.

Particular interest in thrombotic adverse events was a prespecified objective of this study. C1 INH may possess pro- or anticoagulant effects in blood given that it has been described as a weak inhibitor of the formation of plasmin in the fibrinolytic pathway and as a weak inhibitor of coagulation factors XI and XII, respectively.⁷ Results of previous studies in animals and neonates have suggested that doses of C1 INH >200 U/kg (higher than recommended) may be associated with thrombotic events.^{8,9} In the study of neonates who received another plasma-derived C1 INH for an off-label indication, the patients had congenital heart defects, required heart-lung machines, underwent major cardiac corrective surgery, and, in some cases, were septic.⁸ However, high doses of C1 INH have been evaluated in clinical studies of sepsis,^{10,11} myocardial infarction,^{12,13} and ischemia reperfusion injury,¹⁴ which demonstrated improved end-organ function without thrombotic complications. Most recently, Gandhi et al¹⁵ summarized spontaneous adverse event

reports submitted to the US Food and Drug Administration's adverse events database. Ten cases of thrombotic events in patients who received C1-INH-nf were identified (including deep vein thrombosis, embolic stroke and/or intracardiac thrombus, jugular vein thrombosis, myocardial infarction, pulmonary embolism, and transient ischemic attack). The majority of patients had other risk factors for venous or arterial thromboembolism. Although analysis of spontaneously reported adverse event data can result in the detection of a potential safety signal, it cannot establish a causal relationship between thrombotic events and C1 INH-nf therapy.

In our study, the patients received doses of C1 INH-nf up to 2500 U (41 U/kg) every 3 or 4 days for 6 months, and no systemic thrombotic events were observed. One patient reported a single episode of a localized blood clot in a catheter port, which is a common complication for these devices. Although patients with risk factors for thrombotic events should be monitored while receiving C1 INH-nf, the fact that patients in this study received high doses of C1 INH-nf for an extended period of time without systemic thrombotic complications is notable.

This open-label study was not designed or powered to evaluate efficacy as a primary end point. However, patients documented angioedema attacks in diaries, and monthly attack rates were calculated. These data are encouraging in that 9 patients (45%) achieved per-protocol treatment success in experiencing ≤ 1.0 attack/month during dose escalation. An additional 5 patients (25%) were considered to be successfully treated by the investigators or met a *post hoc* definition of a significant reduction in the monthly attack rate from the historic level; most of these patients had final attack rates that were just above the protocol-defined threshold of success (1 attack/month) at their final dose. Importantly, all attacks, regardless of severity, were counted in the analysis of treatment effect.

Six patients were considered to have had treatment failures because they did not show clinically meaningful reductions in their monthly attack rate despite dose escalations. Although the numbers are small, most patients did not have distinguishing demographics or medical history characteristics that could explain their lack of response to treatment. Despite not qualifying as successes, 3 of the 6 patients who had treatment failures had a reduction in the frequency and the severity of their angioedema attacks during dose escalation. However, antibodies to C1 INH were detected in 2 of the patients who failed treatment. Both patients were diagnosed later in life than what is typical for a patient with HAE, and neither patient reported a family history of HAE. Since study completion, a diagnosis of acquired angioedema has been confirmed for one of these patients and suspected for the other. It is possible that these patients' C1 INH deficiency could be the result of acquired angioedema. Lymphoproliferative and autoimmune processes can lead to the production of antibodies to C1 INH and cause acquired angioedema with swelling clinically indistinguishable from HAE.^{16,17} Although neither of these patients had a known lymphoproliferative disorder nor abnormal C1q complement component levels before entering the study, it is possible that the underlying disease was not yet detectable.

Several limitations should be considered when interpreting the results of this study. The efficacy of dose escalation could not be determined because patients were not randomly assigned to increased doses. Although the primary objective of the study was

to evaluate safety, with particular interest in thrombogenicity, the patients with a history of abnormal blood clotting or who used prescription anticoagulant medication were excluded from the study. In addition, as with all studies of rare diseases, the number of patients was small, and the study was not powered to detect infrequent drug-related adverse events. Finally, in the context of a disease that requires lifelong chronic therapy, the maximum duration of follow-up in this study was 48 weeks in a limited number of patients, and, therefore, the adverse events that result from chronic use over the course of many years could not be detected. Consequently, further postmarketing safety surveillance is warranted and is currently ongoing.

In conclusion, we evaluated a treatment algorithm of C1 INH-nf dose escalation that was based on a threshold of adequate control (≤ 1.0 attack/mo). The results showed that doses up to 2500 U every 3 or 4 days were well tolerated and may be considered for patients who do not respond to the approved dose of 1000 U every 3 or 4 days. Further evaluation of treatment optimization of nonresponders is warranted, such as increasing frequency of administration.

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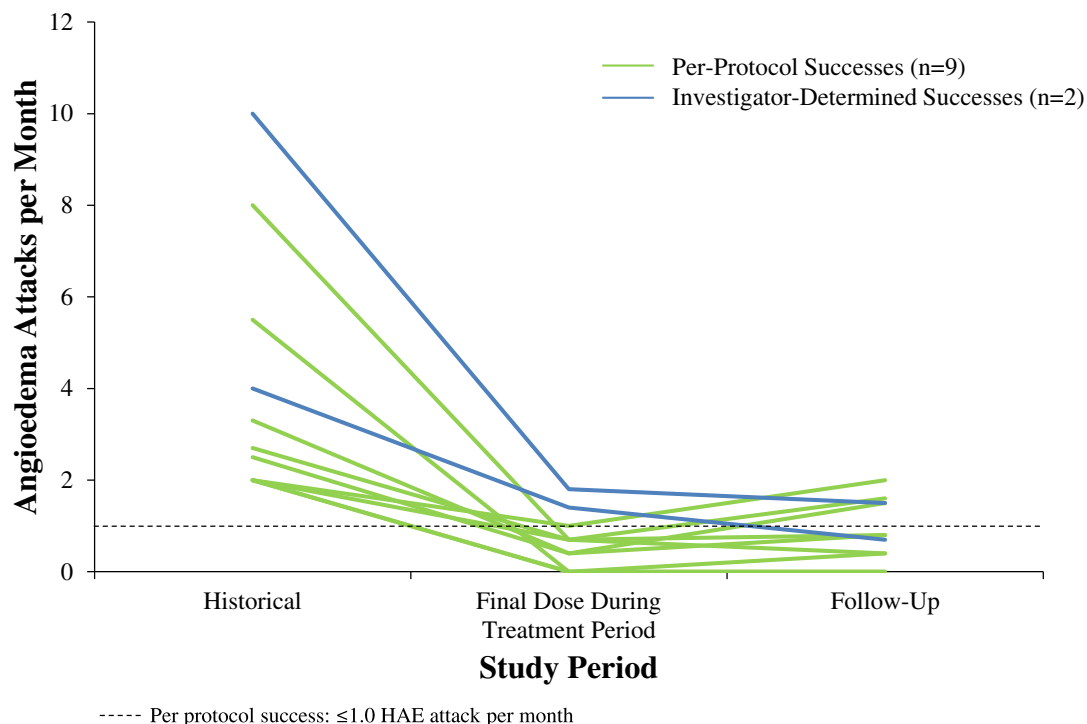


FIGURE E1. The monthly attack rate before the study, during the final dose step, and during follow-up.

TABLE E1. Functional C1 inhibitor levels for each patient at baseline and each dosage step, including follow-up, if applicable

Patient no.	Treatment status at final dose	Functional C1 inhibitor (U/mL)*				Follow-up
		Baseline	1500 U	2000 U	2500 U	
1	Per-protocol success		<0.05			<0.05
2	Per-protocol success	<0.05	<0.05			<0.05
3	Per-protocol success	0.14	0.06			0.09
4	Per-protocol success	<0.05	<0.05			<0.05
5	Per-protocol success	<0.05	<0.05	<0.05	<0.05	<0.05
6	Per-protocol success	0.28	0.94	0.88	0.95	1.16
7	Per-protocol success	0.1	0.39	0.27	0.36	0.13
8	Per-protocol success	0.19	0.29	0.34	0.31	0.4
9	Per-protocol success	0.19	0.4	0.3	0.32	0.48
10	Investigator determined success	<0.05	<0.05			<0.05
11	Investigator determined success	0.13	0.21		0.23	0.38
12	Reduction >1.0	0.19	0.22			
13	Reduction >1.0	0.07		0.19	0.24	
14	Reduction >1.0	<0.05	0.34	<0.05	<0.05	
15	Failure	<0.05	0.41			
16	Failure	0.3	0.18			
17	Failure	<0.05	0.07	0.31	0.34	
18	Failure	0.36	0.06	0.19	<0.05	
19	Failure	<0.05	0.43	0.13	<0.05	
20	Failure	0.1	0.11	<0.05	<0.05	

*Reference range, 0.76-1.33 U/mL.

