Nanofiltered C1-Esterase Inhibitor for the Acute Management and Prevention of Hereditary Angioedema Attacks due to C1-Inhibitor Deficiency in Children

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Objectives To evaluate the use of Cinryze (nanofiltered C1-esterase inhibitor [C1 INH-nf]) for the acute management and prevention of hereditary angioedema attacks in the subgroup of children and adolescents who participated in 2 placebo-controlled and 2 open-label extension studies.

Study design In the acute-attack treatment studies, the efficacy of 1000 U of C1 INH-nf (with an additional 1000 U given 1 hour later if needed) was assessed based on the time to the start of symptomatic relief and the proportion of patients experiencing relief within 4 hours of therapy. In the prophylaxis studies, C1 INH-nf 1000 U was given twice weekly, and efficacy was based on the frequency of attacks.

Results Across 4 studies, 46 children received a total of 2237 C1 INH-nf infusions. The median time to the start of unequivocal relief in the acute-attack treatment study (n = 12) was 30 minutes with C1 INH-nf, compared with 2 hours for placebo. In the open-label extension (n = 22), clinical relief began within 4 hours of therapy in 89% of attacks. In the prophylaxis study (n = 4), the number of attacks was reduced by approximately 2-fold with C1 INH-nf compared with placebo. In the prophylaxis open-label extension (n = 23), the median monthly attack rate decreased from 3.0 before treatment to 0.39 with C1 INH-nf use.

Conclusion In children, C1 INH-nf was well tolerated, provided relief from symptoms of hereditary angioedema attacks, and reduced the rate of attacks. (J Pediatr 2013;162:1017-22).

Hereditary angioedema (HAE) is a rare disease caused by a deficiency in C1-esterase inhibitor (C1 INH),1,2 which plays an important role in regulating the contact and complement systems. Most patients with HAE inherit an autosomal-dominant mutation in the C1 INH gene, although 25% of cases arise from de novo mutations.3 The estimated prevalence of HAE is 1 in 50,000.4,5 HAE is characterized by recurrent, episodic attacks of nonpruritic subcutaneous edema of the skin (face, extremities, trunk, genitalia) or submucosal edema of the gastrointestinal tract or upper airway.1,2,5 In most patients with HAE, clinical symptoms manifest in childhood (typically between age 4 and 11 years), worsen during puberty, and persist throughout life.7-11 Symptoms and frequency of attacks increase during periods of intense physiological development, such as between age 3 and 6 years and at the onset of puberty.7-9 Subcutaneous edema and recurrent colicky abdominal pain caused by gastrointestinal edema are the most common manifestations in children.7,9,11,12 Asphyxia is possible when angioedema involves the upper airway, and can occur more rapidly in children given their narrower airway diameters.8,13 The numerous possible attack triggers include infections, emotional stress, and tissue trauma. Mechanical trauma (eg, bodily contact from play) may be the most common trigger of attacks in children, causing 52.6% of attacks in a population of Hungarian children.8

Although several therapies are available to treat (eg, ecallantide, icatibant, plasma-derived C1 INH) and prevent (eg, antifibrinolytics, attenuated androgens, plasma-derived C1 INH) HAE attacks, children with HAE have different needs than affected adults.8,11,14 For instance, attenuated androgens are associated with decreased growth rate and behavioral issues in children, and thus should be used cautiously.4,8,11 Unfortunately, the diagnosis of HAE is often de-

C1 INH-nf Nanofiltered C1-esterase inhibitor
C1 INH C1-esterase inhibitor
HAE Hereditary angioedema
layed until late adolescence or adulthood, limiting the number of children with HAE who are available for study. As a result, HAE clinical trials to date have included primarily adults, and only limited data are available to guide the treatment of children with HAE.

Cinryze (ViroPharma, Exton, Pennsylvania) is a plasma-derived, nanofiltered C1 INH (C1 INH-nf) approved in the US for routine prophylaxis in adolescents and adults with HAE and in Europe for treatment, routine prevention, and pre-procedural prevention in adults and adolescents with HAE. The successful use of C1 INH-nf in children has been documented in case reports and retrospective studies of actual clinical practice. In prospective, pivotal randomized, placebo-controlled studies and open-label extension studies of C1 INH-nf in patients with HAE, the study population consisted of children, adolescents, and adults. In the present post hoc analysis, we evaluated the use of C1 INH-nf in 46 children who participated in those studies.

Methods

Data from 2 randomized, placebo-controlled studies and their open-label extensions were used in this analysis. One of the studies evaluated the use of C1 INH-nf in acute attacks, and the other study evaluated its use as prophylaxis. Patients aged ≥6 years with a confirmed diagnosis of HAE, including a low C4 level, a normal C1q level, and a low antigenic or functional C1 inhibitor level or a mutation in the C1 inhibitor gene known to cause HAE, were eligible for the randomized, placebo-controlled studies. Patients with a low C1q level, a history of B-cell cancer, presence of antibodies to C1 inhibitor, or a history of allergic reaction to blood or blood plasma products were excluded. Those patients who were randomized in the acute treatment trial (or met the entry criteria after the close of enrollment) and had a history of ≥2 attacks per month were eligible for the placebo-controlled prophylaxis study.

Patients were eligible for the open-label extension studies if they had completed participation in the previous randomized, placebo-controlled studies. In addition, patients aged ≥1 year who were excluded from the placebo-controlled studies for pregnancy or lactation, age <6 years, narcotic addiction, or presence of antibodies to C1 INH were allowed in the open-label studies. Patients who otherwise would have met the entry criteria for the placebo-controlled studies but did not participate in those studies, or who had a diagnosis of HAE based on a family history of HAE as determined by the principal investigator, were also eligible for the open-label studies. To participate in the open-label extension of the prophylaxis study, patients must have had a history 1 or more HAE attacks per month or a history of laryngeal edema.

All patients who participated in the placebo-controlled studies and open-label extension studies provided written informed consent or assent. Clinical protocols and informed consent and assent forms were reviewed and approved by the Institutional Review Board at each investigative site. These trials were registered with ClinicalTrials.gov (NCT00289211, NCT01005888, NCT00438815, and NCT00462709).

In the placebo-controlled acute-attack treatment trial, patients who presented to the study site within 4 hours after onset of a moderate or severe acute attack of the abdomen, face, or external genitalia were randomly assigned to intravenous infusions of placebo or C1 INH-nf 1000 U. The anatomic region most severely affected in the attack was designated as the defining symptom site. Patients with laryngeal attacks were excluded from randomization and were treated with open-label C1 INH-nf. If symptoms at the defining site were not absent or improved within 60 minutes of the initial dose, then a second dose (C1 INH-nf or placebo) was administered. If airway compromise had developed or unequivocal relief had not been achieved within 4 hours, then the patient was offered rescue therapy with open-label C1 INH-nf.

In the open-label extension of the acute-attack treatment study, patients received intravenous infusions of C1 INH-nf 1000 U to treat any laryngeal or moderate or severe gastrointestinal, facial, genitourinary, or extremity attacks. Patients could be treated for multiple attacks. Otherwise, study drug administration and assessments were similar to those of the double-blind study, with the exception that investigators were permitted to discharge patients before completion of the 4-hour posttreatment observation period. In both studies, patients were eligible to receive preprocedural prophylaxis with C1 INH-nf 1000 U before any emergency or noncosmetic surgical or dental procedures.

The placebo-controlled prophylaxis trial consisted of 2 consecutive 12-week treatment periods during which patients received study medication to prevent HAE attacks. Patients were randomly assigned to receive intravenous infusions of C1 INH-nf 1000 U or placebo every 3-4 days. After the first 12-week treatment period, patients crossed over to the alternate treatment arm for the second 12-week treatment period; thus, each individual served as his or her own control. Patients were eligible to receive rescue treatment with open-label C1 INH-nf for acute attacks. Patients (or their parents/guardians) were asked to keep a diary of daily symptoms during both study periods.

In the open-label prophylaxis extension study, intravenous infusions of C1 INH-nf 1000 U were administered every 3-7 days. Patients were also eligible for treatment of acute attacks with the dosing regimen described for the open-label, acute-attack treatment study.

In the acute treatment trials, patients qualitatively assessed themselves for absence or improvement of symptoms before infusion and every 15 minutes after infusion up to 4 hours after the initial infusion or until unequivocal relief of the defining symptom was achieved. Unequivocal relief was defined as 3 consecutive reports of resolved or improved symptoms. Time to unequivocal relief was the time to the first of the 3 consecutive assessments of improvement. In the acute treatment open-label extension, patients were also evaluated for the criteria of clinical relief, defined as either unequivocal relief or 1 or 2 consecutive assessments with improvement, followed by cessation of symptom assessment. (In the open-label
extension, patients could be discharged before complete resolution of symptoms at the investigator’s discretion.) Patients for whom no posttreatment assessment data were collected were excluded from the analysis of clinical relief.

In the prophylaxis trials, patients kept a daily diary of symptoms. The number, duration, and severity of attacks during the treatment periods were assessed. Attack severity was scored on a 3-point scale, with 1 indicating mild, 2 moderate, and 3 severe.

In these studies, safety was evaluated by assessing adverse events, monitoring vital signs, and performing viral safety testing and anti-C1 INH antibody testing. C1 INH functionality was assessed and antigen and C4 levels were measured by Specialty Laboratories (Valencia, California). Testing for IgA, IgM, and IgG antibodies to C1 INH was conducted using a validated assay (assay 5839, antibodies against C1-inhibitor enzyme-linked immunosorbent assay; Sanquin Diagnostic Services, Amsterdam, The Netherlands).

Data from the children (aged <18 years) who participated in these studies were compiled and evaluated. Because this study was conducted post hoc, all data summaries are descriptive in nature. Changes in functional and antigenic C1 INH and C4 levels were evaluated before and after infusion. Summary statistics were prepared for all adverse events and all adverse events related to the study drug.

## Results

Forty-six children and adolescents ranging in age from 2 to 17 years received a total of 2237 C1 INH-nf infusions in the 4 studies, including 49 infusions in 3 patients aged 2-5 years, 1056 infusions in 17 patients aged 6-11 years, and 1132 infusions in 26 patients aged 12-17 years. The numbers of patients in each study are summarized in Figure 1 (available at www.jpeds.com).

### Acute-Attack Treatment

**Placebo-Controlled.** Twelve children (5 aged 6-11 years and 7 aged 12-17 years) were treated for a qualifying event (7 with C1 INH-nf and 5 with placebo) in the placebo-controlled acute-attack treatment study. Another 3 children received open-label C1 INH-nf for treatment of laryngeal angioedema and/or before emergency surgical procedures. With the exception of 1 attack in each treatment group with moderate facial swelling, the defining symptom site for all attacks was gastrointestinal pain. Unequivocal relief of the defining symptom began within 4 hours after initial treatment in 5 of 7 patients receiving C1 INH-nf, compared with 2 of 5 patients receiving placebo (Table I). For those patients who achieved unequivocal relief, the median time to the start of unequivocal relief was 0.5 hours (range, 0.25-2.25 hours) with C1 INH-nf, compared with 2 hours (0.5-3.5 hours) with placebo. One patient in the C1 INH-nf group who did not achieve unequivocal relief within 4 hours subsequently achieved complete resolution of the attack at 11.75 hours after the initial treatment.

The ages (9 and 16 years) and weights (34.4 and 56.7 kg) of the 2 patients who did not achieve the start of unequivocal relief within 4 hours after the initial C1 INH-nf treatment were within the ranges of the overall pediatric population. The median age of patients who received C1 INH-nf was 11 years (range, 6-16 years), and the median weight was 56.7 kg (range, 24.5-85.3 kg).

Of the 6 patients who received C1 INH-nf and achieved relief and/or resolution of the attack, 3 received 1 dose and 3 received 2 doses. Four children in the placebo group required rescue (open-label) C1 INH-nf and/or narcotics; 1 patient received rescue C1 INH-nf (1 dose), 2 patients received rescue narcotics, and 1 patient received both rescue C1 INH-nf (2 doses) and narcotics. In comparison, 2 children in the C1 INH-nf group received rescue treatment with C1

### Table I. Unequivocal relief of the defining symptom within 4 hours after start of the first dose of C1 INH-nf during the acute-attack treatment studies stratified by age

<table>
<thead>
<tr>
<th>Defining symptom site</th>
<th>Placebo</th>
<th>C1 INH-nf</th>
<th>Placebo</th>
<th>C1 INH-nf</th>
<th>Placebo</th>
<th>C1 INH-nf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled study</td>
<td>n = 0</td>
<td>n = 0</td>
<td>n = 1</td>
<td>n = 4</td>
<td>n = 4</td>
<td>n = 3</td>
</tr>
<tr>
<td>Laryngeal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2/3 (66.7)</td>
<td>1/4 (25.0)</td>
<td>2/3 (66.7)</td>
</tr>
<tr>
<td>Facial</td>
<td>0</td>
<td>0</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extremity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All symptoms</td>
<td>0</td>
<td>0</td>
<td>1/1 (100)</td>
<td>3/4 (75.0)</td>
<td>1/4 (25.0)</td>
<td>2/3 (66.7)</td>
</tr>
<tr>
<td>Open-label extension</td>
<td>n = 1*</td>
<td>4/7 (57.1)</td>
<td>35/36 (97.2)</td>
<td>20/23 (87.0)</td>
<td>0/1*</td>
<td>25/28 (89.3)</td>
</tr>
<tr>
<td>All symptoms</td>
<td>69/76 (90.3)</td>
<td>39/44 (88.6)</td>
<td>77/77 (100)</td>
<td>67/67 (85.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This 2-year-old patient received two 500 U doses of C1 INH-nf 1 hour apart for treatment of a facial attack. The patient had 1 report of symptom relief (“present, symptoms better”) 3 hours after start of the first 500 U dose of C1 INH-nf, but underwent no subsequent symptom assessments. Thus, the endpoint requirement of 3 consecutive reports of improved/absent symptoms was not met. However, the patient was discharged from the study center 3 hours and 50 minutes after the start of C1 INH-nf therapy.
INH-nf at 4 hours and 17 hours (each 1 dose), respectively, and none required narcotics.

Open-Label. In the open-label extension, 22 children who were evaluated for efficacy experienced a total of 121 attacks; gastrointestinal (53%) and facial swelling (23%) were most common (Figure 2). Eighty-eight attacks were treated with 1 dose of C1 INH-nf, and 33 attacks were treated with 2 doses. Unequivocal relief started within 1 hour after the initial dose of C1 INH-nf in 79% of attacks and within 4 hours after the initial dose in 89% of attacks (Table I). In the majority of laryngeal attacks (67%; 6 of 9), unequivocal relief began within 1 hour after the initial dose, and no child required intubation or hospitalization for a laryngeal attack. The response rate within 4 hours and the time to start of relief remained consistent irrespective of attack number or location. Two patients received only preprocedural doses (1000 U each) and were not included in the efficacy dataset.

A total of 117 attacks were evaluated for clinical relief; only attacks with at least 1 posttreatment assessment were included in this analysis. Of these, 113 attacks (97%) had clinical relief within 4 hours after the initial dose of C1 INH-nf. Analysis of the 117 attacks with posttreatment symptom assessment revealed that only 4 attacks (2 gastrointestinal and 2 facial) did not achieve clinical relief within 4 hours. Patients with up to 8 attacks were evaluated, and the median time to the start of clinical relief did not appear to increase during subsequent attacks (Table II). Mean changes in functional C1 INH activity, C1 INH antigen levels, and C4 levels from pretreatment to 1 hour posttreatment for the first attack are summarized in Table III (available at www.jpeds.com).

Preprocedural Prophylaxis

Eight children received C1 INH-nf before a total of 40 procedures, 90% of which were dental procedures. A single 1000 U dose was administered before 39 procedures, and 2 1000 U doses were administered over a 48-hour period for 1 procedure (labor/delivery). Only 1 HAE attack was reported within 72 hours after preprocedural dosing.

Routine Prophylaxis

Placebo-Controlled. Four children (aged 9–17 years) enrolled in and completed the pivotal prophylaxis trial. The children had a nearly 2-fold reduction in number of HAE attacks while receiving C1 INH-nf prophylaxis compared with the time period during which they received placebo (mean number of attacks, 7.0 vs 13.0 over 12 weeks). The mean severity score during each arm of the crossover was 1.6. The mean duration of attacks was 2.3 days during C1 INH-nf therapy and 2.6 days during placebo therapy. Patients were eligible to receive open-label C1 INH-nf infusions for treatment of acute attacks during the double-blind treatment periods. A mean of 6.8 open-label doses of C1 INH-nf were required for treatment of attacks while patients were receiving active prophylaxis treatment with C1 INH-nf, compared with 15.0 open-label doses while patients were receiving placebo. The mean duration of swelling in the 2 groups was 9.0 days and 20.8 days, respectively.

Open-Label. Twenty-three children received open-label C1 INH-nf prophylaxis. Table IV summarizes the exposure to C1 INH-nf, which varied among patients. Patient-reported median monthly attack rate before enrollment was 3.0 (range, 0.5–28.0) and decreased to 0.39 (range, 0–3.36) during C1 INH-nf prophylaxis. The majority of patients (87%; 20 of 23) experienced ≤1 attack per month, and 22% (5 of 23) reported no attacks during the study period.

C1 INH and C4 levels were measured every 12 weeks during the open-label prophylaxis study. Data for 5 or more patients were available for weeks 0, 12, 24, 36, 48, 60, and 72. During these time points, mean increases in C1 INH antigen from pretreatment to 1 hour posttreatment ranged from 6.7 to 10.1 mg/dL. Mean percentage increases in functional C1 INH ranged from 27.0% to 45.9%. C4 values at 1 hour posttreatment did not change significantly from pretreatment values (mean change, -1.5 to 0.3 mg/dL); this finding was not surprising, however, given that C4 response to C1 INH administration had been previously shown to peak at 48 hours (data on file [2006-5 Study]; ViroPharma).
Due to C1-Inhibitor Deficiency in Children

Nanofiltered C1-Esterase Inhibitor for the Acute Management and Prevention of Hereditary Angioedema Attacks

Discussion

Because HAE is a rare disease, only limited information on the treatment of affected children is available. In this post hoc analysis of data from 4 prospective clinical trials, we report the experience of 46 children and adolescents with HAE who received a total of 2237 C1 INH-nf infusions, making this the largest compilation of pediatric patient data from prospective HAE clinical trials published to date. Results from the placebo-controlled, acute-attack treatment study show that 71% of children who received C1 INH-nf for treatment of an acute attack achieved unequivocal relief within 4 hours, which was consistent with the rate observed in the study population as a whole (60%).

Similar results were observed in the placebo-controlled prophylaxis study. The average number of attacks during the 12-week treatment period for children (7.0 in the C1 INH-nf group and 13.0 in the placebo group) was consistent with those for the study population as a whole (6.26 and 12.73, respectively). When interpreting the results of the randomized controlled prophylaxis study, it is important to note that all patients received open-label C1 INH-nf for treatment of acute attacks, even during the placebo phase of the double-blind treatment.

The results of the open-label studies showed that most children who received C1 INH-nf for treatment of acute attacks experienced relief within 1 hour of treatment, and those who received prophylaxis therapy had a reduced monthly attack rate. Taken together, these data offer a substantive body of evidence supporting the clinical utility of C1 INH-nf in children with HAE.

C1 INH function and antigen levels after treatment of children were consistent with those observed for the overall study populations that included adults. Neither weight nor age appeared to affect clinical response. In the treatment of acute attacks, patients who did not show improvement within an hour after the initial 1000 U dose received a second 1000 U dose. Most attacks (71%) were adequately treated with the initial dose of C1 INH-nf, which was also consistent with the overall rate for the open-label acute treatment study (69%). However, if weight or age had an effect on C1 INH levels or response, then fewer children would be expected to require a second dose compared with adults. This provides further evidence that neither weight nor age influenced the likelihood of response to the initial dose. Across the entire clinical development program, no relationship was observed between weight or pharmacokinetics and efficacy (data on file; ViroPharma). This finding is not surprising, given the significant interpatient and intrapatient variability for both the baseline level of C1 INH and the rate of C1 INH consumption, both of which are independent of body weight.

C1 INH-nf was well tolerated, with no HIV or viral hepatitis transmission or detection of clinically relevant anti-C1 INH antibodies in these studies.

Table IV. Summary of exposure to C1 INH-nf and frequency of HAE attacks during the open-label prophylaxis study

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Number of patients on C1 INH-nf</th>
<th>Duration of dosing period (days), median (range)</th>
<th>Total number of prophylaxis infusions</th>
<th>Prophylaxis infusions per patient, median (range)</th>
<th>Attacks per month per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5</td>
<td>2</td>
<td>155 (22-288)</td>
<td>46</td>
<td>23.0 (4-42)</td>
<td>0.69 (0-136)</td>
</tr>
<tr>
<td>6-11</td>
<td>9</td>
<td>301 (64-923)</td>
<td>732</td>
<td>41.0 (10-258)</td>
<td>0.35 (0-453)</td>
</tr>
<tr>
<td>12-17</td>
<td>12</td>
<td>273 (97-760)</td>
<td>760</td>
<td>68.0 (15-121)</td>
<td>0.71 (0-897)</td>
</tr>
</tbody>
</table>

Safety

No adverse events were reported in the pivotal acute-attack treatment trial. In the open-label treatment extension, 9 of 24 patients (38%) reported adverse events. With the exception of streptococcal pharyngitis (2 patients), all other adverse events (ie, upper abdominal pain, acne, constipation, cough, eczema, hand fracture, pharyngolaryngeal pain, rash, sinus congestion, sinusitis, upper respiratory tract infection, bacterial vaginitis, and vulvovaginal mycotic infection) were reported by 1 patient each. No adverse events in the open-label treatment extension were deemed related to C1 INH-nf by the principal investigator.

One patient in the pivotal prophylaxis study experienced pyrexia that was considered possibly related to the study drug. In the open-label prophylaxis extension, 17 of 23 patients (74%) reported adverse events. Two patients reported a total of 3 adverse events that were considered related to C1 INH-nf; 1 patient had headache and nausea, and the other had infusion-site erythema. All 3 of these events were of mild severity.

No serious or severe adverse events were considered by the investigator to be related to C1 INH-nf, and no adverse events led to discontinuation of treatment. There was no evidence of HIV or viral hepatitis transmission or development of clinically relevant anti-C1 INH antibodies in these studies.

Discussion

Because HAE is a rare disease, only limited information on the treatment of affected children is available. In this post hoc analysis of data from 4 prospective clinical trials, we report the experience of 46 children and adolescents with HAE who received a total of 2237 C1 INH-nf infusions, making this the largest compilation of pediatric patient data from prospective HAE clinical trials published to date. Results from the placebo-controlled, acute-attack treatment study show that 71% of children who received C1 INH-nf for treatment of an acute attack achieved unequivocal relief within 4 hours, which was consistent with the rate observed in the study population as a whole (60%).

Similar results were observed in the placebo-controlled prophylaxis study. The average number of attacks during the 12-week treatment period for children (7.0 in the C1 INH-nf group and 13.0 in the placebo group) was consistent with those for the study population as a whole (6.26 and 12.73, respectively). When interpreting the results of the randomized controlled prophylaxis study, it is important to note that all patients received open-label C1 INH-nf for treatment of acute attacks, even during the placebo phase of the double-blind treatment.

The results of the open-label studies showed that most children who received C1 INH-nf for treatment of acute attacks experienced relief within 1 hour of treatment, and those who received prophylaxis therapy had a reduced monthly attack rate. Taken together, these data offer a substantive body of evidence supporting the clinical utility of C1 INH-nf in children with HAE.

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C1 INH-nf was well tolerated, with no HIV or viral hepatitis transmission or detection of clinically relevant anti-C1 INH antibodies. Many adverse events reported in children were associated with common childhood infections, including pharyngitis, sinusitis, and other upper respiratory tract infections. No deaths, thrombotic events, or related serious adverse events were reported. Overall, no clinically meaningful trends in frequency or types of adverse events were observed in children compared with the overall study population.

Some limitations of the present study must be considered when interpreting the results. Primarily, a post hoc analysis cannot replace a well designed, prospective, randomized, placebo-controlled study in children with HAE. However, given the current availability of approved therapies and the overall rarity of the disease, exposing a large number of children to placebo would not be ethical. Furthermore, weight-controlled, dose-response studies of therapies for rare diseases in children, particularly those younger than 10
years, are not logistically feasible because of the large numbers of patients required to sufficiently power such studies. In the absence of such well-controlled pediatric studies, the purpose of the present post hoc analysis was to summarize the outcomes of the pediatric subgroups from larger studies that were part of an overall development program for C1 INH.

The recent publication of consensus guidelines for the treatment of children with HAE highlights the importance of making these data available in the scientific literature.

We thank Scientific Therapeutics Information (Springfield, New Jersey) and Scott Newcomer (ViroPharma) for assistance with manuscript preparation. A list of investigators who had pediatric patients in the Cinryze Study Groups LEVP 2005-1/A, LEVP 2005-1/B, LEVP 2006-1, and LEVP 2006-4 is available at www.jpeds.com (Appendix).

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References

The following investigators had pediatric patients enrolled in Cinryze Study Groups LEVP 2005-1/A, LEVP 2005-1/B, LEVP 2006-1, and LEVP 2006-4:

James Baker, Allergy, Asthma and Dermatology Associates, Lake Oswego, OR; Leonard Bielory, University of Medicine and Dentistry of New Jersey, Newark, NJ; Eric Brestel, Allergy Partners of Eastern Carolina, Greenville, NC; Paula Busse, Mount Sinai School of Medicine, New York, NY; William Cartwright, Cornerstone Healthcare, Parkersburg, WV; Linda Cox, Nova Southeastern University Osteopathic College of Medicine, Fort Lauderdale, FL; Timothy Craig, Pennsylvania State University, Hershey, PA; Mark Davis-Lorton, Winthrop University Hospital, Mineola, NY; Richard Gower, Marycliff Allergy Specialists, Galveston, TX; Michael Greenfield, Olathe Medical Center, Olathe, KS; J. Andrew Grant, University of Texas Medical Branch, Galveston, TX; David Hurewitz, Allergy Clinic of Tulsa, Tulsa, OK; Joshua Jacobs, Allergy and Asthma Clinical Research, Walnut Creek, CA; Robert J. Lazar, Grand Traverse Allergy, Traverse City, MI; William Lumry, Allergy and Asthma Research Associates, Dallas, TX; Michael Manning, Allergy and Immunology Associates, Scottsdale, AZ; Tina Merritt, Allergy and Asthma Associates, Bentonville, AR; James Moy, Rush University Medical Center, Chicago, IL; Ayre Rubinstein, Albert Einstein College of Medicine, Bronx, NY; Manav Singla, Upper Chesapeake Medical Center Ambulatory Care, Bel Air, MD; Patrick Stoy, MeritCare Medical Group, Fargo, ND; Arthur Vegh, Allenmore Medical Center, Tacoma, WA; and Martha White, Institute for Asthma and Allergy, Wheaton, MD.
**Table III.** Mean changes in C1 INH levels between pre-treatment and 1 hour post-treatment during the first attack evaluated in the open-label extension of the acute-attack treatment study

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>2-5</th>
<th>6-11</th>
<th>12-17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Change</td>
<td>n</td>
</tr>
<tr>
<td>Functional C1 INH, %</td>
<td>1</td>
<td>89.0 (29.62)</td>
<td>6</td>
</tr>
<tr>
<td>C1 INH antigen, mg/dL</td>
<td>1</td>
<td>15.0 (3.05)</td>
<td>7</td>
</tr>
<tr>
<td>C4, mg/dL</td>
<td>1</td>
<td>0.0 (0.53)</td>
<td>7</td>
</tr>
</tbody>
</table>

Values are mean (SD) change from the pretreatment value to 1 hour posttreatment.

**Figure 1.** Number of pediatric patients in each study.