Preventing Hereditary Angioedema Attacks in Children Using Cinryze®: Interim Efficacy and Safety Phase 3 Findings

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was the number of angioedema attacks per month. Results: Six females with HAE type I and a median age of 10.5 years received 2 doses of C1-INH (500 and 1,000 U). The mean (SD) difference in the number of monthly angioedema attacks between the baseline observation period and the treatment period was −1.89 (1.31) with 500 U and −1.89 (1.11) with 1,000 U. During the treatment periods, cumulative attack severity, cumulative daily severity, and the number of attacks needing acute treatment were lower. No serious adverse events or study drug discontinuations occurred. Conclusions: Interim findings from this study indicate that routine prevention with intravenous administration of C1-INH is efficacious, safe, and well tolerated in children ≥6 years of age.

Introduction

Hereditary angioedema (HAE), a rare disease with an estimated prevalence of 1 in 50,000 [1], is characterized by episodic swelling of the skin, abdomen, and larynx [2, 3]. HAE types I and II are identified by low total levels and...
nonfunctionality of the C1 inhibitor (C1-INH), respectively, accounting for approximately 85 and 15% of cases [4]. Untreated HAE attacks can last for 2–5 days [5]. The clinical presentation of HAE, including age of symptom onset, anatomical location, frequency, and severity [6–8], are diverse, and about 50% of patients can experience potentially fatal laryngeal attacks [9, 10]. Examples of attack triggers are stress, hormonal changes, surgical or dental procedures, infection, or hormonal therapy for women such as oral contraceptives or hormone replacement therapy [11–14].

To minimize disease burden and improve quality of life [15, 16], prophylaxis is recommended. Three commercially available human plasma-derived C1-INHs [17–19] for HAE are available with small differences in purity, antigen-activity ratio, and specific activity [20]. However, Cinryze® (Shire ViroPharma Inc., Lexington, MA, USA), a nanofiltered human plasma-derived C1-INH, is the only approved C1-INH for routine prophylaxis in adolescents and adults in the USA, and in pediatric patients (≥6 years of age) with severe and recurrent attacks, adolescents, and adults in the EU [19]. Cinryze is also approved in the EU for the on-demand treatment of acute attacks and for preprocedure prevention of attacks in patients (≥2 years of age). It is administered intravenously to patients as a fixed dose rather than a body weight-adjusted dose of 1,000 U every 3–4 days in adolescents and adults and 500 U or 1,000 U if needed in pediatric patients. Previous studies including 2 placebo-controlled and 2 open-label extension studies involving 46 patients indicated that C1-INH is safe and efficacious in this group [21].

The objective of this ongoing phase 3 study is to assess the safety and relative efficacy of 2 different C1-INH doses in preventing HAE attacks in children aged 6–11 years who have recurrent attacks. Herein we report the interim results for the first 6 patients who completed the study.

### Patients and Methods

This is an ongoing randomized phase 3 single-blind crossover study involving 4 US sites and 3 EU sites (NCT02052141). Data for this interim analysis were collected between March 2014 and April 2015. Parents or legal guardians provided written informed consent, and patients assented to participate in this study. The study protocol, informed consent, and subject recruitment information were approved by the ethics committees before study initiation. This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice, the principles of the Declaration of Helsinki, and other applicable local ethical and legal requirements. Patient selection was based on the following: age ≥6 and <12 years, a confirmed HAE type I or II diagnosis, a functional C1-INH level that was <50% of normal levels, and a monthly average of ≥1.0 attacks classified as moderate, severe, or needing acute treatment in the 3-month period before screening. The requirement for monthly attack frequency was ≥2.0 in Germany, and patients were required to be ≥25 kg in weight. Patients with a history of hypercoagulability, allergic reaction to C1-INH products, or an acquired angioedema diagnosis were excluded.

Following screening, there was a 12-week baseline observation period to monitor patients’ HAE attacks. Patients who experienced ≥1.0 monthly attacks classified as moderate or severe or that necessitated acute treatment during the baseline observation period (≥2.0 monthly attacks in Germany) were then randomly assigned to 1 of 2 intravenous C1-INH doses, 500 or 1,000 U, administered every 3–4 days for 12 weeks. Patients switched to the alternative dose for a second 12-week period. Patients were not randomized if they had an active infectious illness or a fever within 24 h, or signs and/or symptoms of an angioedema attack within 2 days. Patients and their parents or caregivers were blinded to the treatment sequence.

Parents or caregivers used electronic study diaries to record study information, and all patients were followed up 1 week and 1 month after treatment initiation. Attack severity was rated as mild,
moderate, or severe, corresponding to severity scores of 1, 2, and 3, respectively. Adverse events were recorded. Physical examinations, vital sign measurement, clinical laboratory tests, and testing for anti-C1-INH antibodies were also performed.

The primary efficacy endpoint was the number of attacks per month in a 12-week treatment period. Secondary efficacy endpoints, also calculated for each patient in a 12-week period, were cumulative attack severity (the sum of the maximum symptom severity score recorded for each attack), cumulative daily severity (the sum of the maximum severity scores recorded for each day of symptoms), and the number of attacks requiring acute treatment. These values were normalized for the number of days a patient participated in a given period and expressed as a monthly frequency.

Results

Six female patients with HAE type I and a median (range) age of 10.5 (7–11) years have completed the study (Table 1). In the 3 months before screening, patients experienced a mean (SD) of 4.2 (1.2) attacks per month, and all patients reported ≥1 angioedema attack affecting the gastrointestinal tract or abdomen. After the 12-week baseline observation period, 2 patients received 500 U C1-INH (for 12 weeks) followed by 1,000 U C1-INH (for 12 weeks), and 4 patients received these treatment doses in the opposite sequence. Each patient received 23–24 injections of 500 U C1-INH and 22–24 injections of 1,000 U C1-INH. Four patients (67%) had ≥1 concomitant medications; however, only 2 patients (33%) received concomitant medications to manage HAE attacks and its associated symptoms. One patient received concomitant treatment with a single intravenous C1-INH dose (1,000 U) for a mild upper airway attack. Another patient received Baralgina (with fenpiverinium bromide, metamizole sodium, and pitofenone hydrochloride as major components) to manage a severe gastrointestinal attack.

The mean (SD) number of attacks after the observation period was 2.26 (1.62) attacks per month. The mean (SD) difference (normalized per month) in the number of attacks between the observation period and the treatment period was –1.89 (1.31) with 500 U and –1.89 (1.11) with 1,000 U (Fig. 1a), which is a reduction of –84.8 and –88.1%, respectively. During both treatment periods, cumulative attack severity, cumulative daily severity, and the number of attacks needing acute treatment were also lower (Fig. 1).

Five patients experienced a total of 55 treatment-emergent adverse events (TEAEs): 25 TEAEs in 4 patients while receiving 500 U C1-INH and 30 TEAEs in 5 patients while receiving 1,000 U C1-INH. The adverse event profiles for both doses were comparable. No serious adverse events, thrombotic events, thromboembolic events, or study drug discontinuations occurred. One patient had 2 severe angioedema attacks during treatment with 500 U C1-INH.
C1-INH. Adverse events of fatigue and irritability in 2 patients each were related to the study drug (Table 2). No patients reported a TEAE during infusion of either C1-INH dose, and the majority of TEAEs (HAE attack, nasopharyngitis, upper respiratory tract infection, fatigue, and irritability) occurred within 24 h after administration. In addition, all patients tested negative for anti-C1-INH antibodies, and no clinically relevant abnormalities were found in clinical laboratory tests or vital signs.

**Table 2.** Treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Type of TEAE (within 24 h after administration)</th>
<th>12 weeks 500 U C1-INH (n = 6)</th>
<th>12 weeks 1,000 U C1-INH (n = 6)</th>
<th>total (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type</td>
<td>4 (66.7)</td>
<td>5 (83.3)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>HAE attack</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Irritability</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>TEAE related to the study drug</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Irritability</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>TEAE by maximum severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (16.7)</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>TEAE during study drug administration</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any serious event</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to study drug discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as n (%). HAE, hereditary angioedema; TEAEs, treatment-emergent adverse events.

* One patient reported 2 severe TEAEs that were HAE attacks during treatment with 500 U of a nanofiltered C1 inhibitor (C1-INH).

**Discussion**

A study of Danish patients with HAE found that the mean annual attack rate, without prophylaxis, was 17 per year, with broad variation between patients [22]. This interim analysis of an ongoing phase 3 study showed that intravenously administered C1-INH (500 or 1,000 U) was safe and well tolerated in children aged 7–11 years with HAE. The same formulation of C1-INH (1,000 U) was previously evaluated in a placebo-controlled, crossover study of mostly adult patients with a history of ≥2 monthly attacks [23]. The number of attacks per 12-week period was significantly reduced from 12.7 with placebo to 6.3 with C1-INH. The severity and number of attacks needing open-label rescue therapy were also reduced. An open-label 2.6-year extension study in patients with a mean (SD) age of 36.5 (16.5) years showed that C1-INH prophylaxis reduced the median number of monthly attacks by 93.7% (3.00–0.19) [24]. A post hoc analysis of data from 4 prospective clinical trials was performed to evaluate the efficacy of C1-INH (1,000 U) for acute treatment and prophylaxis in a pediatric subgroup [21]. This post hoc analysis showed that in the placebo-controlled trial, 4 patients (9–17 years of age) had their number of HAE attacks almost halved from 13.0 with placebo to 7.0 with C1-INH prophylaxis. In addition, 23 patients aged 2–17 years in the open-label extension study [21] had a reduction in their median (range) monthly attacks from 3.0 (0.5–28.0) before enrollment to 0.39 (0–3.36) after prophylaxis. However, this was a post hoc analysis rather than a clinical trial in children with HAE. The interim analysis described here, however, shows a similar reduction in the monthly number of attacks from a mean (SD)
of 2.262 (1.622) at baseline to 0.372 (0.470) with 500 U C1-INH and 0.372 (0.573) with 1,000 U C1-INH. This is an 84% reduction in the number of attacks relative to baseline. Moreover, the attacks that occurred were generally less severe and fewer required rescue medication.

C1-INH is used as prophylaxis because it acts on the complement and contact plasma cascades, thereby reducing bradykinin release (the main pathologic mechanism in HAE) [25]. At the end of the study, 4 patients (66.7%) were attack free after prophylaxis at either dose. Previous studies have also shown that patients still experience HAE attacks while on C1-INH prophylaxis. In the placebo-controlled phase 3 study [23], 18% of 22 patients were attack free after prophylaxis [26]. In the open-label extension study [24], 35% of 146 patients were attack free following prophylaxis. Although routine prophylaxis with C1-INH reduces attack severity and frequency, it does not completely prevent breakthrough attacks. Since administered C1-INH doses are unable to return functional C1-INH to normal levels in all patients, it is likely that individualization of the dose or administration frequency will be needed to achieve optimal responses in some patients [23]. In support of this, another study found that escalating the C1-INH dose to 2,500 U every 3 or 4 days for those who are not responsive to 1,000 U is well tolerated [27]. In addition, C1-INH was shown in a previous study to have a positive impact on the quality of life of patients [28].

Our study indicates that regular C1-INH infusions provided effective prophylaxis in this group of pediatric patients with a considerable pretreatment disease burden. The target sample size in this study is small but appropriate given the rarity of HAE and the specific age group. Although this is an interim analysis, the results support previous clinical studies [21] indicating that C1-INH may have a beneficial, prophylactic role in HAE management in children.

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References


