


# A Review of Randomized Controlled Trials of Hereditary Angioedema Long-Term Prophylaxis with C1 Inhibitor Replacement Therapy: Alleviation of Disease Symptoms Is Achievable

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**Abstract:** Through its fluctuating disease activity and unpredictable attacks, hereditary angioedema (HAE) imposes a substantial patient burden. To minimize HAE burden and improve quality of life, treatment should involve individualized management strategies that address on-demand therapy and short-term/long-term prophylaxis. Goals of long-term prophylaxis include reducing the number, severity, and burden of HAE attacks. The best characterized forms of HAE arise from deficiency or dysfunction of C1-inhibitor (C1-INH; types I/II), and C1-INH replacement therapy is a first-line intervention for on-demand (acute) treatment of HAE attacks, short-term prophylaxis before high-risk procedures, and long-term prophylaxis. Randomized, double-blind, placebo-controlled crossover trials have shown dose-dependent efficacy with plasma-derived C1-INH (pdC1-INH) 40–60 IU/kg subcutaneously, pdC1-INH 1000 U intravenously, and recombinant human C1-INH (rhC1-INH) 50 IU/kg (maximum 4200 IU) intravenously, all administered twice weekly, as long-term prophylaxis in patients with a history of 2 to  $\geq 4$  attacks/month. Overall, up to 83% (pdC1-INH 60 IU/kg) of patients experienced an HAE attack reduction threshold of  $\geq 70\%$ , and up to 58% (pdC1-INH 60 IU/kg) achieved an attack reduction threshold of  $\geq 90\%$ . Lower-dose intravenous pdC1-INH therapy (1000 U) was seemingly less effective, with 45% of 22 patients experiencing an HAE attack reduction threshold of  $\geq 70\%$ , and up to 23% achieving an attack reduction threshold of  $\geq 90\%$ . Higher-dose intravenous rhC1-INH 50 IU/kg (maximum, 4200 IU) twice weekly was of intermediate benefit. Despite a baseline mean attack frequency of 17.9 (during the 3 months prior to study treatment) and a mean attack frequency during a 4-week placebo period of 7.2, 52% of 23 patients experienced  $\geq 70\%$  reduction in attack frequency and 26% of 23 patients experienced  $\geq 90\%$  reduction in attack frequency. The increasing patient percentages treated with C1-INH replacement therapy as long-term prophylaxis meeting these high thresholds reinforces hopes and expectations that “attack freedom” is achievable, including for those with moderate or severe disease.

**Keywords:** hereditary angioedema, complement C1 inhibitor protein, clinical trial design, clinical outcomes, prophylaxis

## Introduction

Hereditary angioedema (HAE) is a group of genetic diseases characterized by fluctuating and unpredictable episodes of angioedema (ie, attacks) that, if uncontrolled, can have a profound negative effect on patient lives.<sup>1</sup> The frequency of HAE attacks can vary widely; some patients experience a few attacks annually, whereas others experience multiple attacks each month.<sup>1–3</sup> HAE attacks manifest as reversible edema (angioedema) that affects cutaneous or submucosal tissue at various body sites.<sup>4</sup> Commonly affected areas include the extremities (eg, hands and feet), gastrointestinal tract, urogenital region, face, and upper airway.<sup>2,3</sup> Attacks involving the hands and feet can lead to functional impairment, and attacks affecting the abdomen may be associated with very painful, debilitating colic, with vomiting, hypotension, and

complete disablement for a day or longer.<sup>2</sup> Furthermore, obstruction of the airway due to laryngeal HAE attacks can be life-threatening.<sup>2</sup> In patients with HAE due to a deficiency in functional levels of C1 esterase inhibitor (C1-INH; type I [deficiency] and type II [dysfunction] HAE), there is abnormal coagulation, and increased plasmin activity probably contributes to the angioedema tendency.<sup>2,5</sup> Consequently, increased production of vasoactive mediators (notably bradykinin) within microvascular beds leads to sudden, reversible capillary hyperpermeability with consequent edema of local tissues.<sup>2,6</sup>

HAE continues to present challenges due to the heterogeneity of its clinical course, including frequency, location, severity, and unpredictability of attacks and variable duration of symptom-free intervals.<sup>1,3</sup> C1-INH deficiency affects multiple biochemical pathways, including complement activation through the classical and lectin complement pathway, the contact and kallikrein/kinin system through effects on kallikrein and activated factor XII, the intrinsic coagulation pathway through activated factor XI, and fibrinolysis through the plasminogen-plasmin system.<sup>5,7-9</sup> Even during attack-free periods, C1-INH deficiency in patients with HAE will typically be observed in the presence of low levels of C4 and sometimes C2; these features indicate continuous inappropriate activation of the early classical complement pathway, with overconsumption of these complement components.<sup>8</sup> Decreased function of C1-INH with subsequent dysregulation of the classical and lectin complement pathways may lead to increased co-occurrence of autoimmune disease in patients with HAE and C1-INH deficiency.<sup>10</sup> It has been known for many years that patients with HAE have a higher risk of developing immunoregulatory disorders.<sup>11</sup> To an extent, this effect may be related to acquired deficiencies of the early classical pathway components C2 and C4, which may lead to autoimmune disorders in the presence of C1-INH deficiency.<sup>12</sup> However, C1-INH deficiency does not deplete C1q in most patients.<sup>10</sup>

Treatment of HAE should involve individualized management strategies addressing on-demand/acute therapy, short-term and long-term prophylaxis, to minimize disease burden and improve patient-related quality of life.<sup>2,13</sup> On-demand treatments of HAE attacks include C1-INH replacement therapy (plasma-derived C1-INH [pdC1-INH] or recombinant human C1-INH [rhC1-INH]); ecallantide, a kallikrein inhibitor; and icatibant, a bradykinin B2 receptor antagonist.<sup>2,13</sup> Despite differences in trial design, review of clinical trial data is consistent with a dose-dependent benefit of C1-INH in time to response and response rates.<sup>14</sup> Administration of C1-INH replacement therapy as short-term prophylaxis is recommended before medical or dental procedures that may trigger an HAE attack (eg, dental surgery or endoscopic procedures).<sup>2</sup> Limited observational evidence suggests that efficacy of short-term preprocedural prophylaxis improves with increased dose.<sup>15</sup> Long-term prophylaxis is considered in patients with recurrent episodes of HAE to reduce the frequency, duration, and severity of attacks, as well as to minimize the impact of the disease on daily activities.<sup>2,13</sup> Given the expansion of therapeutic options for long-term prophylaxis during the last several years, alongside short-term prophylaxis and on-demand treatments for attacks, the goal of achieving control of HAE attacks and normalization of patients' lives is moving in a positive direction.<sup>2,13</sup> First-line long-term prophylactic treatment for HAE includes intravenous and subcutaneous pdC1-INH; subcutaneous lanadelumab, a monoclonal antibody that targets plasma kallikrein; and oral berotralstat, a small-molecule inhibitor of plasma kallikrein.<sup>2,13</sup> In many cases, breakthrough HAE attacks occur despite prophylaxis. However, complete elimination of HAE attacks is the goal of modern prophylactic treatments.

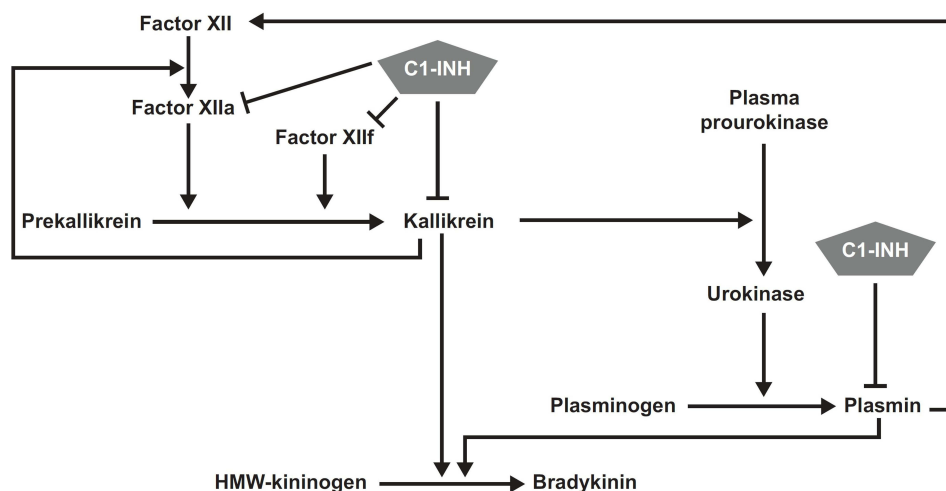
There is considerable global experience (>40 years) in treating C1-INH deficiency by replacing C1-INH protein levels (eg, on-demand therapy) in patients with HAE. Pursuit of this possibility and of the role of C1-INH replacement therapy as long-term prophylaxis depends on addressing continued challenges in HAE management through careful interpretation of randomized controlled trial (RCT) data. Such interpretation may be confounded by differences in RCT patient populations analyzed, routes of administration, pharmacokinetic and pharmacodynamic considerations, and product forms and availability (human plasma collection or recombinant technology). Differences in route of administration and in baseline attack frequency further confound comparisons, such that any conclusions drawn should be considered hypothesis-generating only, pending appropriate head-to-head trials. Data from these trials suggest that with adequate dosing and frequency of administration, even in patients with high symptomatic HAE activity, the burden of disease could potentially be minimized. Direct and indirect comparisons of different prophylactic doses of C1-INH support a dose–response relationship for efficacy in long-term prophylaxis, as well as for acute and short-term prophylaxis. This review will examine data from RCTs evaluating administration of C1-INH replacement therapy as long-term HAE

prophylaxis in patients with HAE, aiming to generate preliminary hypothesis-generating answers to questions such as, “is a higher C1-INH dose more effective than a lower dose”, and “what degree of attack frequency alleviation can be achieved?” However, further work is required before we can fully answer the important question, “is efficacy of prophylaxis impacted by baseline attack frequency?”

## Long-Term Prophylaxis to Address HAE Pathophysiology

Because contact and kallikrein/kinin pathway–targeted therapies cannot address the increased risk of autoimmunity, C1-INH replacement has an advantage in this respect. Of further interest might be reports of increased proportion of malignant versus reduced incidence of cardiovascular causes of death in patients with HAE (despite the use of attenuated androgens) compared with the general population.<sup>16</sup> C1-INH concentrates are perhaps the most physiological approach to HAE management because these therapies directly replace the missing protein in the various cascades.<sup>17</sup> Notably, C1-INH replacement therapy acts to restore equilibrium to the contact and kallikrein/kinin activation system.<sup>9</sup> This is achieved by pluripotent regulation of the activation of kallikrein, factor XII (Figure 1) and other inflammatory pathways, which may affect bradykinin production, most notably plasmin.<sup>17</sup> Overall, this concept is speculative, as the benefit of C1-INH replacement in autoimmunity, malignancy, and cardiovascular disease has not been thoroughly investigated.

Given that the plasma half-life of endogenous C1-INH is approximately 67 to 72 hours,<sup>7</sup> long-term prophylaxis with pdC1-INH at a dose (eg, 60 U/kg subcutaneously, twice weekly) that delivers a near equivalent plasma half-life is effective for reducing the frequency of HAE attacks.<sup>2,13,18</sup> As well, subcutaneous administration of C1-INH replacement therapy may provide more sustained steady-state plasma levels of C1-INH relative to intravenous administration. This has been hypothesized as potentially improving symptom control.<sup>2</sup> However, questions about the pharmacokinetics and pharmacodynamics of C1-INH replacement therapies in plasma and at physiologically relevant sites of action, namely the endothelium, remain to be answered. A plasma functional C1-INH activity of 38% (0.38 U/mL) has been proposed as a threshold level for conferring substantial protection against HAE attacks.<sup>19</sup> However, other studies suggest that for pdC1-INH, at least, functional plasma C1-INH levels need to be in the normal range to provide complete protection.<sup>14,18</sup> The concept that replacement therapy should restore C1-INH functional activity to the normal range is intuitively attractive, although additional research is required to validate that plasma concentrations correlate sufficiently with attack prevention.<sup>14,20</sup> Moreover, plasma functional C1 inhibitor levels are not informative when rhC1-INH is used, despite good observed efficacy.<sup>21</sup> Questions about a correlation between C1-INH plasma concentrations and clinical effectiveness have been raised, given the efficacy of rhC1-INH as prophylaxis despite its relatively short plasma half-life compared with pdC1-INH therapies.<sup>20</sup>



**Figure 1** Production of bradykinin through kallikrein-dependent reactions. Reprinted from *J Allergy Clin Immunol*, Vol 126, no 5, Kaplan AP, Enzymatic pathways in the pathogenesis of hereditary angioedema: the role of C1 inhibitor therapy, pp918-925, Copyright 2023, with permission from Elsevier.<sup>17</sup>

**Abbreviation:** C1-INH, C1 esterase inhibitor.

## RCTs of Long-Term Prophylaxis with C1-INH Replacement Therapy

Two pdC1-INH therapies (intravenous Cinryze and subcutaneous Haegarda) have been studied in RCTs and are approved for use as long-term HAE prophylaxis in children, adolescents, and adults.<sup>13,18,22–26</sup> The intravenous recombinant C1-INH replacement therapy rhC1-INH, also known as conestat alfa (Ruconest), has been investigated as long-term prophylaxis for HAE<sup>21</sup> but is currently only indicated as on-demand (acute) treatment of HAE attacks in adolescents and adults.<sup>27</sup> Differences among long-term prophylaxis RCTs make direct comparisons across C1-INH replacement therapies difficult (eg, patient inclusion criteria, baseline disease severity, study design, and phase, dose, and duration of treatment). Overall HAE severity (rather than just attack frequency) is difficult to quantify in the absence of a validated biomarker as well as a comprehensive clinical disease burden/quality of life tool.<sup>1</sup> Therefore, RCTs of C1-INH replacement therapies have largely assessed efficacy by measuring changes in the frequency of HAE attacks.

All RCTs of C1-INH replacement therapies for long-term HAE prophylaxis have been randomized, double-blind, placebo-controlled crossover trials, with no active comparator trials published to date (Table 1).<sup>18,21,22</sup> Differences in study design among the 3 trials include the dosing (eg, unit dose; fixed or weight-based dosing) length of treatment (eg, 4–16 weeks), washout period duration (eg, 1–2 weeks), and number of treatment periods (eg, 2–3). One crossover trial compared a fixed dose of intravenous pdC1-INH 1000 U or placebo administered every 3–4 days.<sup>22</sup> Subsequent trials used a weight-based dosing regimen.<sup>18,21</sup> One trial evaluated subcutaneous pdC1-INH 40 IU/kg and 60/kg IU twice weekly,<sup>28</sup> and the other evaluated twice-weekly and once-weekly intravenous rhC1-INH 50 IU/kg (maximum, 4200 IU).<sup>21</sup> Inclusion criteria across the 3 RCTs varied in age (eg, inclusion/exclusion of preadolescent children) and baseline HAE attack frequency (Table 1). Individuals included in the RCT of rhC1-INH prophylaxis included a population experiencing a higher rate of attacks (ie, severe disease), with patients having a mean of 17.9 attacks during the 3 prior months (range, 12–33) and a mean attack frequency of 7.2 during the 4-week placebo treatment period (Table 1).<sup>21</sup> Patients included in the subcutaneous pdC1-INH trial had a lower mean of 8.8–10.8 attacks in the 3 months before screening and a monthly attack rate during placebo treatment of 3.61–4.03.<sup>18</sup> Pre-screening attack rates were not reported

**Table 1** Study Design Elements in Randomized Controlled Trials of Long-Term Prophylaxis with C1-INH Replacement Therapies in Adult Patients with HAE

| Parameter     | Plasma-Derived C1-INH IV <sup>22</sup>   | Plasma-Derived C1-INH SC <sup>18</sup>  | Recombinant Human C1-INH IV <sup>21</sup>  |
|---------------|--|---|--|
| Study design  | Randomized, double-blind, placebo-controlled crossover (phase 3)<br>2 parallel groups treated in 2 consecutive 12-week periods | Randomized, double-blind, placebo-controlled crossover (phase 3)<br>2 parallel dose groups treated in 2 consecutive 16-week periods | Randomized, double-blind, placebo-controlled crossover (phase 2)<br>3 parallel groups sequenced through 3 treatments during 3 consecutive 4-week treatment periods (6 sequences)   |
| Randomization | 1:1  | 1:1:1:1   | 1:1:1:1:1:1  |
| Treatment     | 2 Periods<br>pdC1-INH 1000 U or placebo IV q 3–4 days for 12 weeks   | 2 Periods (2-week washout period between treatments)<br>pdC1-INH (40 IU/kg or 60 IU/kg) or placebo twice weekly for 16 weeks        | 3 Periods (1-week washout period between treatments)<br>rhC1-INH 50 IU/kg (<84 kg; 4200 U ≥84 kg) twice weekly for 4 weeks or<br>rhC1-INH 50 IU/kg (<84 kg body weight; 4200 U ≥84 kg) once weekly plus placebo once weekly for 4 weeks or<br>Placebo twice weekly for 4 weeks |

(Continued)

Table 1 (Continued).

| Parameter                 | Plasma-Derived C1-INH IV <sup>22</sup>   | Plasma-Derived C1-INH SC <sup>18</sup>  | Recombinant Human C1-INH IV <sup>21</sup>   |
|---------------------------|--|---|---|
| Eligibility criteria      | Age: ≥6 years (n = 22)<br>HAE with low C4 level, normal C1q level, and low antigenic or functional C1-INH level or mutation in C1-INH gene known to cause HAE<br>HAE attacks: history of ≥2 attacks/month <sup>a</sup> | Age: ≥12 years (n = 90)<br>HAE type 1 or type 2 with functional C1-INH activity <50% and C4 antigen level below normal level<br>HAE attacks for entry into run-in period: ≥4 attacks during a 2-month consecutive period, within 3 months of screening <sup>b</sup><br>HAE attacks during 8-week run-in period: ≥2 attacks within any consecutive 4 weeks or ≥1 attack during first 2 weeks | Age: ≥13 years (n = 32)<br>Functional C1-INH level <50% of normal and history of frequent HAE attacks<br>HAE attacks:<br>≥4 attacks/month for ≥3 consecutive months before study entry <sup>c</sup> |
| Baseline attack frequency | Not specified  | Attacks during 3 months before screening, mean (SD)<br>40 IU dose group (n = 45): 10.8 (6.7)<br>60 IU dose group (n = 45): 8.8 (6.4)  | Attacks during 3 months before study (n = 32)<br>Mean (SD): 17.9 (7.2)<br>Median (range): 14.5 (12–33)  |

**Notes:** <sup>a</sup>HAE prophylaxis with stable dosing of androgens or antifibrinolytics permitted. <sup>b</sup>HAE prophylaxis with stable dosing of oral medications (eg, androgens, tranexamic acid, progestins) permitted if received stable dose for 3 months before screening, planned to continue throughout trial, and attack frequency met. Patients who received C1-INH for routine prophylaxis within 3 months before screening and those with significant history of poor response to C1-INH therapy were excluded. <sup>c</sup>HAE prophylaxis with stable dosing of androgens or antifibrinolytics permitted if attack frequency met.

**Abbreviations:** C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; IV, intravenous; pdC1-INH, plasma-derived C1-INH; rhC1-INH, recombinant human C1-INH; SC, subcutaneous.

for the intravenous pdC1-INH trial, but patients receiving placebo treatment experienced 12.73 attacks over 12 weeks, suggesting a monthly attack rate of approximately 4.2.<sup>22</sup> A small pediatric trial compared 2 doses of intravenous pdC1-INH administered twice weekly in children with even lower prospectively observed baseline median attack rates of 5.5 (range, 3–48) per 3 months, or ~1.8 per month.<sup>25</sup> Based on weight tables from the US Centers for Disease Control and Prevention, the pdC1-INH dose ranges for the pediatric trial are approximately equivalent to 12 U/kg to 25 U/kg (500 U dose) or 23.8 U/kg to 50 U/kg (1000 U dose). For adults, doses of 1000 U correspond to 12.5 U/kg on average. However, given that 42.4% of US adults (2017–2018) and 10.7% to 30.6% of adults in the European Union (2019) were considered obese (ie, body mass index ≥30),<sup>29,30</sup> 12.5 to 50 U/kg is likely to be an overestimate of the dose received by many patients.

## Implications of Efficacy Results and Further Research Opportunities

Long-term prophylaxis with C1-INH replacement therapy was efficacious for reducing the number of HAE attacks and was generally well tolerated in patients with HAE (Table 2).<sup>18,21,22</sup> A dose response was observed in the 2 trials evaluating >1 dose concentration (Table 2).<sup>18,21</sup> Evaluation of the percentage of patients achieving a particular threshold of HAE attack reduction provides additional insights into the efficacy of long-term prophylaxis with C1-INH replacement therapy (Table 3; Figure 2).<sup>18,21,22,25</sup> In particular, for patients with moderate-to-severe baseline attack severity, C1-INH replacement therapy is effective at the different thresholds of HAE attack reduction examined (Figure 2). Data suggest that the goal of long-term prophylaxis could be refocused toward freedom from HAE attacks, even for those with severe baseline disease. Overall, up to 83% (pdC1-INH 60 IU/kg) of patients experienced an HAE attack reduction threshold of ≥70%, and up to 58% (pdC1-INH 60 IU/kg) achieved an HAE attack reduction threshold of ≥90% (Table 3),<sup>18</sup> with a clear dose-response observed for subcutaneous dosing; further, administration of intravenous C1-INH exhibited similar dose responsiveness (Table 3).<sup>21,22</sup> Percentages of patients treated with C1-INH replacement therapy as long-term prophylaxis meeting these high thresholds raises hopes and expectations that the goal of “attack freedom” is achievable, including for those with moderate-to-severe disease. Intravenous prophylaxis also showed dose-dependent benefit: mean normalized attack rates with intravenous pdC1-INH 1000 U twice

**Table 2** Primary Efficacy and Safety Outcomes in Randomized Controlled Trials of Long-Term HAE Prophylaxis with CI-INH Replacement Therapy

| Parameter                | Plasma-Derived CI-INH IV <sup>22</sup>  | Plasma-Derived CI-INH SC <sup>18</sup>  | Recombinant Human CI-INH IV <sup>21</sup>   |
|--------------------------|---|---|---|
| Primary endpoint         | Number of patient-reported angioedema attacks; normalized for number of days each patient participated during that period   | Number of investigator-reported angioedema attacks; analyzed without imputation for missing data  | Number of patient-reported angioedema attacks within each 4-week treatment period; sensitivity analysis conducted using last observation carried forward imputation to evaluate whether missing data occurred at random   |
| Primary endpoint results | Time-normalized attack rates/month in both crossover periods, mean<br>Placebo (n = 11): 4.24<br>pdCI-INH IV (n = 11): 2.09<br>Reduction in HAE attacks vs placebo, mean (n = 11): 50.8% | Number of time-normalized attacks/month, mean<br><u>40 IU/kg dose group</u><br>Placebo (n = 44): 3.61<br>pdCI-INH SC (n = 43): 1.19<br>Within-patient difference: -2.42, p < 0.001<br><u>60 IU/kg dose group</u><br>Placebo (n = 42): 4.03<br>pdCI-INH SC (n = 43): 0.52<br>Within-patient difference: -3.51, p < 0.001<br>Reduction in HAE attacks vs placebo, mean:<br>40 IU (n = 38): 55%<br>60 IU (n = 40): 84% | Number of attacks over 1 month, mean <sup>a</sup><br>Placebo (n = 31): 7.2<br>rhCI-INH twice-weekly (n = 31): 2.7<br>Mean difference vs placebo: -4.4 (p < 0.0001)<br>Placebo (n = 31): 7.2<br>rHCI-INH once-weekly (n = 31): 4.4<br>Mean difference vs placebo: -2.8 (p < 0.0004)<br>Reduction in HAE attacks vs placebo, mean:<br><u>ITT</u><br>rhCI-INH twice-weekly dose (n = 31): 63.3%<br>rhCI-INH once-weekly dose group (n = 31): 34.9%<br><u>PP</u><br>rhCI-INH twice-weekly (n = 23): 72.1%<br>rhCI-INH once-weekly (n = 23): 44.4% |
| Safety results           | No anaphylactic reactions<br>No CI-INH-related thrombotic complications   | No anaphylactic reactions<br>No CI-INH-related thrombotic complications   | No hypersensitivity or systemic allergic reactions, including anaphylactic reactions<br>No thrombotic or thromboembolic events  |

**Note:** <sup>a</sup>ITT population (n=32) with exclusion of 1 patient who had been randomized but did not receive study medication.

**Abbreviations:** CI-INH, CI esterase inhibitor; HAE, hereditary angioedema; ITT, intention-to-treat; IV, intravenous; pdCI-INH, plasma-derived CI-INH; PP, per protocol; rhCI-INH, recombinant human CI-INH; SC, subcutaneous.

**Table 3** Additional Efficacy Endpoints in Randomized Controlled Trials of Long-Term HAE Prophylaxis with CI-INH Replacement Therapy

| Parameter   | Plasma-Derived CI-INH IV <sup>22</sup>          | Plasma-Derived CI-INH SC <sup>18</sup>   | Recombinant Human CI-INH IV <sup>21</sup>   |
|---|---|--|---|
| ≥50% Reduction in attacks versus placebo (95% CI)         | pdCI-INH 1000 U (n = 11): 50%                   | 40 IU/kg (n = 43): 76% (62–87)<br>60 IU/kg (n = 43): 90% (77–96)                   | <u>ITT (n = 31)</u><br>rhCI-INH twice weekly: 74% (57–86)<br>rhCI-INH once weekly: 42% (26–59)<br><u>PP (n = 23)</u><br>rhCI-INH twice weekly: 96% (79–99)<br>rhCI-INH once weekly: 57% (37–74) |
| ≥70% or ≥75% Reduction in attacks versus placebo (95% CI) | ≥75% reduction<br>pdCI-INH 1000 U (n = 11): 45% | ≥70% reduction<br>40 IU/kg (n = 43): 67% (52–79)<br>60 IU/kg (n = 43): 83% (68–91) | ≥75% reduction <sup>a</sup><br><u>PP (n = 23)</u><br>rhCI-INH twice weekly: 52% (33–71)<br>rhCI-INH once weekly: 26% (12–46)  |

(Continued)

Table 3 (Continued).

| Parameter   | Plasma-Derived CI-INH IV <sup>22</sup> | Plasma-Derived CI-INH SC <sup>18</sup>                           | Recombinant Human CI-INH IV <sup>21</sup>  |
|---|--|--|--|
| ≥90% Reduction in attacks versus placebo (95% CI) | pdCI-INH 1000 U (n = 11): 23%          | 40 IU/kg (n = 43): 43% (29–58)<br>60 IU/kg (n = 43): 58% (42–72) | PP (n = 23) <sup>a</sup><br>rhCI-INH twice weekly: 26%<br>rhCI-INH once weekly: 9% |

Notes: <sup>a</sup>Data on file. Pharming Healthcare, Inc.

Abbreviations: CI-INH, CI esterase inhibitor; HAE, hereditary angioedema; ITT, intention-to-treat; IV, intravenous; pdCI-INH, plasma-derived CI-INH; PP, per protocol; rhCI-INH, recombinant human CI-INH; SC, subcutaneous.

weekly were lower than with placebo during the 12-week treatment period (6.26 vs 12.73 attacks, respectively; difference, 6.47 attacks [95% CI, 4.21–8.73];  $p < 0.001$ ).<sup>22</sup> While not directly comparable, use of rhCI-INH in higher doses of 50 U/kg once or twice weekly produced a greater reduction in attack rates compared with placebo (4.4 or 2.7 attacks with rhCI-INH once or twice weekly, respectively, vs 7.2 attacks [placebo]) (Table 2).<sup>21</sup> Overall, 45% of the patients experienced an HAE attack reduction threshold of ≥70% with pdCI-INH 1000 U twice weekly (for adults, approximately 12.5 U/kg twice weekly), while 26% and 52% of the patients receiving rhCI-INH 50 U/kg weekly or twice weekly, respectively, achieved a reduction threshold of ≥75% (Table 3). An HAE attack reduction threshold ≥90% was achieved by 23% of the patients receiving pdCI-INH 1000 U twice weekly, and by 9% and 26% of the patients receiving rhCI-INH 50 U/kg weekly or twice weekly, respectively (Table 3). The majority of patients (70%) who received escalating doses of IV pdCI-INH (1500 U to 2500 U) experienced improvement in the number of HAE attacks compared with the number of attacks experienced while receiving IV pdCI-INH 1000 U.<sup>31</sup> Preadolescent children with a lower baseline attack rate who were administered IV pdCI-INH 500 U or 1000 U twice weekly also appeared to show more complete attack control at the higher dose: 58.3% vs 91.7% of the patients experienced an HAE attack reduction threshold of ≥70%, and 33.3% vs 50% of the patients experienced an HAE attack reduction threshold of ≥90%.<sup>25</sup> These studies strongly support a dose–response for C1 inhibitor efficacy in long-term prophylaxis.

It is also worthwhile to place in context the potential pharmacokinetic differences among the C1-INH replacement therapies. While the plasma half-life of endogenous C1-INH is approximately 67–72 hours,<sup>7</sup> the mean half-life

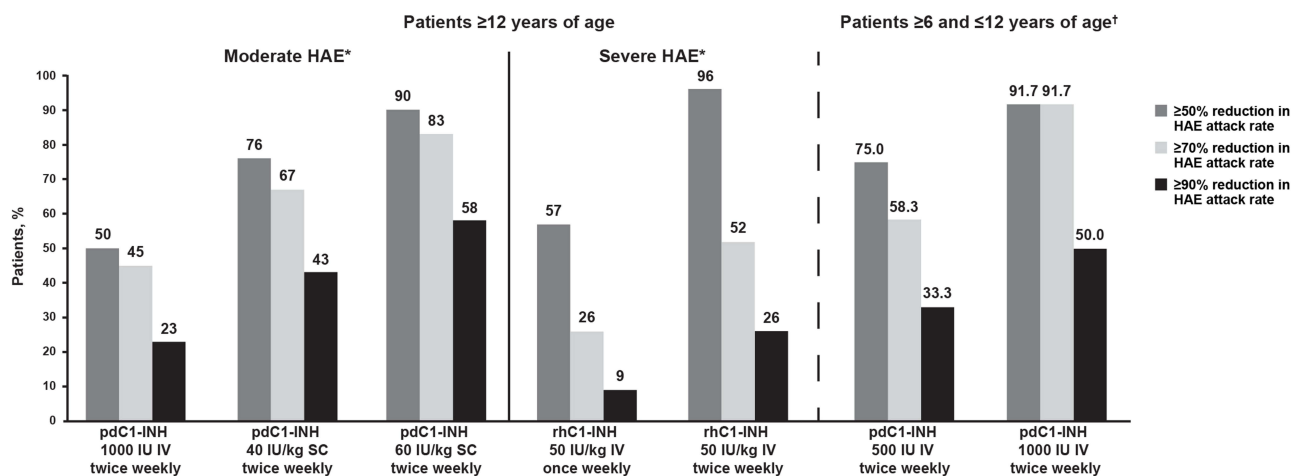


Figure 2 Mean percentage reductions in acute hereditary angioedema attack rates with C1-INH replacement therapies, by dose.

Notes: \*Based on HAE attack severity (severity scores: 1 [mild], 2 [moderate], 3 [severe]) during placebo treatment period in patients ≥12 years of age.<sup>18,21</sup> †Average HAE attack severity during 3-month period before screening for patients ≥6 and ≤12 years of age was moderate (75% [n = 9]) or severe (25% [n = 3]).<sup>25</sup> Data from Longhurst H et al. *N Engl J Med*. 2017;376(12):1131–40<sup>18</sup> and Aygören-Pürsün E, et al. *Pediatr Allergy Immunol*. 2019;30(5):553–561,<sup>25</sup> with additional study data.

Abbreviations: CI-INH, CI esterase inhibitor; HAE, hereditary angioedema, IV, intravenous; pdCI-INH, plasma-derived CI-INH; rhCI-INH, recombinant human CI-INH; SC, subcutaneous.

for C1-INH replacement agents has been reported to range from 69 (95% CI, 24–251) hours with subcutaneous pdC1-INH 60 IU/kg,  $56 \pm 36$  hours with intravenous pdC1-INH 1000 U, and  $2.4 \pm 0.6$  hours with intravenous rhC1-INH 50 IU/kg.<sup>27,32,33</sup> The short plasma half-life of rhC1-INH has been attributed to glycosylation of the recombinant protein and interactions with specific receptors in the liver.<sup>20</sup> Because the clinical efficacy of this agent does not appear to be adversely affected by this short plasma half-life, and population pharmacokinetic analysis confirms the restoration of normal C1-INH levels, albeit briefly, in 94% of the treated patients, the relevance of plasma half-life to clinical efficacy with rhC1-INH remains an open question.<sup>20</sup> Because C1 inhibitor is active on the endothelial surface, plasma levels are likely to be, at best, a surrogate for effective activity at the relevant site, and in the case of rhC1-INH, of no benefit at all.<sup>21</sup> Therefore, any reliance on plasma concentrations of C1-INH replacement therapies as a predictor of efficacy in the long-term prophylaxis of HAE attacks needs to be considered in context. Further research is needed on the possible mechanism and sites of action of rhC1-INH to help explain the lack of correlation between its plasma half-life and clinical efficacy as long-term prophylaxis, possibly in the context of a future phase 3 clinical trial.<sup>20</sup>

The RCT data support that C1-INH replacement therapy is an effective tool for long-term prophylaxis in the management of HAE. Reductions in HAE attack frequency of  $\geq 90\%$  are achievable and could represent freedom from disease activity in clinical practice. Further exploration of the potential impact of patient-related and disease-related variables (eg, baseline disease frequency) would be valuable to optimize long-term management of HAE and minimize risk of breakthrough HAE attacks. Questions that remain to be answered include whether baseline HAE attack frequency is important; if genetic variation in the individual physiological pathways for bradykinin production affects treatment efficacy; and if more frequent C1-INH replacement dosing correlates with better HAE attack control. In conclusion, data from C1-INH replacement RCTs suggest that with adequate dosing and frequency of administration, even for patients with highly symptomatic HAE activity, potentially minimizing the burden of this disease is achievable.

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