

Hereditary angioedema: Validation of the end point time to onset of relief by correlation with symptom intensity

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ABSTRACT

Time to onset of symptom relief in hereditary angioedema (HAE) is a common primary end point in clinical studies but it has never been validated by correlation with the course of HAE symptoms. This study was designed as a retrospective validation of the primary end point for a placebo-controlled phase II/III study in patients with HAE. Ninety-eight abdominal attacks were treated with 10 or 20 U/kg of a highly purified C1 esterase inhibitor (C1-INH) concentrate or placebo. The primary end point was the time to onset of symptom relief, as determined by the patients. Patients assessed the intensity of the symptoms of pain, nausea, vomiting, cramps, and diarrhea over time. By Spearman rank correlation, the primary end point was compared with the time to first reduction of (1) any symptom intensity, (2) the sum of symptom intensity scores, and (3) the intensity of the last symptom present at baseline. The C1-INH, 20 U/kg, and placebo groups were compared by one-sided two-sample Wilcoxon tests. The time to first reduction in intensity of the last symptom present at baseline had the highest correlation with the primary end point ($r = 0.77$). The time to onset of symptom relief and the time to the first reduction in intensity of the last symptom were significantly shorter for the C1-INH, 20 U/kg, group compared with placebo ($p = 0.009$ and $p = 0.0036$, respectively). The association with the intensity of single symptoms confirmed that the time to onset of symptom relief is an appropriate end point for assessing the efficacy of C1-INH therapy.

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Hereditary angioedema (HAE) is a rare autosomal-dominant disorder caused by deficiency (type I) or dysfunction (type II) of C1 esterase inhibitor (C1-

INH).^{1,2} A third form of HAE (type III), which is the most rare, is characterized by normal complement levels and may be caused by mutations in the factor XII gene.³ C1-INH, belonging to the serine protease inhibitor family, is involved in the regulation of vascular permeability by inhibition of the complement system, the contact system, and the intrinsic coagulation system.⁴

Clinically, HAE is characterized by skin swellings, abdominal pain attacks, and rare episodes of life-threatening upper airway obstruction.^{5,6} HAE attacks typically worsen during the first 24 hours after onset and then slowly subside over 24–72 hours.⁶ The frequency of attacks is variable, typically ranging from one attack per year to weekly attacks in some patients.⁷

Replacement therapy with i.v. pasteurized C1-INH concentrate is recommended as first-line therapy for the treatment of acute attacks of HAE and for short-term prophylaxis.^{6–9} Berinert (CSL Behring, Marburg, Germany) is a purified, double virus-inactivated (*i.e.*, by two independent steps), human plasma-derived C1-INH concentrate that replaces the missing or physiologically inactive protein and is approved in Europe, the United States, and Japan for the treatment of acute HAE attacks.¹ More than 300,000 treatments using this product have been administered during >20 years of use with an excellent safety profile.¹ Most recently, the placebo-controlled International Multicenter Prospective Angioedema C1-INH Trial 1 (I.M.P.A.C.T.1) study established 20 U/kg as a safe and effective dosing

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recommendation for the treatment of acute HAE attacks with C1-INH concentrate.¹⁰

No objective clinical test exists for quantifying the effect of HAE treatments and most signs and symptoms of an HAE attack are known only to the patient (such as internal swelling, stomach cramping, or pain).¹¹ Hence, self-assessment of the disease state by HAE patients is the standard parameter in clinical studies. The primary efficacy end point in the I.M.P.A.C.T.1 study was the time to onset of overall symptom relief as determined by the patients.¹⁰ The time from the start of treatment to the patient-reported onset of symptom relief has been widely used for the evaluation of HAE therapies (*e.g.*, Waytes *et al.*,¹² Kunschak *et al.*,¹³ and subsequent studies summarized by Frank¹⁴) and is accepted by regulators in the United States¹⁵ and Europe.¹⁶ However, no validation of this commonly used end point by correlation of the general symptom relief to single symptom characteristics has been reported to date. It is still unknown whether the onset of general symptom relief is robustly associated with single symptom characteristics.

Based on data obtained in the placebo-controlled I.M.P.A.C.T.1 study, we retrospectively validated the primary end point by correlation with the course of predefined symptoms of abdominal HAE attacks. We compared the time to onset of symptom relief with (1) the time to the *first* decrease in intensity of any symptom, (2) the time to the first decrease of the *sum* of intensity scores of all symptoms, and (3) the time to decrease in intensity of the *last* symptom present at baseline.

METHODS

Study Design

I.M.P.A.C.T.1 was a multinational, parallel-group, randomized, placebo-controlled, three-arm, double-blind, phase II/III study conducted between August 2005 and December 2007 to investigate the efficacy and safety of C1-INH concentrate in the treatment of acute HAE attacks. The protocol was approved by the independent Ethics Committee or Institutional Review Board at each participating center and written informed consent was obtained from each patient or, in the case of a minor, from a legally acceptable representative. The safety of the study was overseen by an independent data and safety monitoring board.

The efficacy and safety results of this study have been reported recently.¹⁰ Here, we report on a retrospective validation of the primary efficacy end point, *i.e.*, the time to onset of symptom relief, by correlation with the course of individual symptoms of abdominal HAE attacks that were prospectively evaluated during the study.

Patients were included in the study if they had laboratory-confirmed C1-INH deficiency (type I or II

HAE), were at least 6 years of age, and were then treated on presentation of an acute moderate to severe abdominal or facial attack within 5 hours of the attack attaining moderate intensity (as assessed by the patient and confirmed by the investigator). The main exclusion criteria were a history of hypersensitivity to C1-INH concentrates, acquired and all other types of angioedema, abdominal pain not associated with C1-INH deficiency, use of pain medication during the current attack, and treatment with any C1-INH concentrate or any other drug for acute angioedema, or with fresh frozen plasma or native plasma, within 7 days before the start of treatment in the current study. Only abdominal attacks were analyzed for the retrospective end point validation because predefined symptoms for these attacks had been evaluated during the study.

Patients were randomized by a centralized, validated, computerized system and received a single i.v. infusion of either C1-INH (Berinert), at a dose of 10 or 20 U/kg, or placebo. Each patient was treated for only a single abdominal or facial attack because it was suspected that patients and physicians were able to discern the treatment group after the first treatment.

Patients were observed for at least 4 hours after the start of treatment, after which they could be discharged from the center if they had reported onset of symptom relief. After 4 hours, patients who reported insufficient or no symptom relief could receive a second dose of double-blind treatment (called "rescue study medication") as follows: C1-INH, 20 U/kg, for patients on placebo; C1-INH, 10 U/kg, for patients on C1-INH, 10 U/kg; and placebo for patients on C1-INH, 20 U/kg. Open-label C1-INH concentrate could be administered in emergency situations (*i.e.*, for life-threatening laryngeal edema).

Study Outcomes

The primary end point was the time from the start of treatment to the onset of symptom relief, as determined by the patients' response to a standard question posed by the investigator. After the start of treatment, each patient was asked the following question every 15 minutes for the first 2 hours; every 30 minutes for the next 2 hours; and at 5, 6, 7, 8, 12, 16, 20, and 24 hours after start of administration of the study medication: "Taking into account all of the symptoms you experienced with this HAE attack, are you confident that it is starting to improve?" If the answer was "yes" for two consecutive time points, the questioning was stopped. The time of onset of relief was defined by the time determined at the first of the two consecutive "yes" responses.

For the primary efficacy analysis in the I.M.P.A.C.T.1 study, the time to onset of symptom relief was set to 24 hours (*i.e.*, the poor/failure outcome) if a patient re-

ceived rescue study medication before the onset of relief or received narcotic analgesics, antiemetics, or open-label C1-INH or fresh frozen plasma during the first 4 hours after treatment, to provide a stringent analysis ("with imputation of rescue medication") with regard to the comparison between treatment groups.¹⁰ In an additional analysis, the time to onset of symptom relief was evaluated as reported by the patients, ignoring rescue medication ("without imputation of rescue medication"). Although both analyses were performed for the validation of the primary end point, the analysis without imputation of rescue medication was the primary analysis for the end point validation, because it accurately reflects the time to overall symptom relief irrespective of the administration of rescue medication. Furthermore, this analysis can better be associated with the course of intensity of the individual symptoms as reported by the patients in a real-time setting. The imputation of the time assessment for treatment failure plays a role for comparisons between treatment groups but is irrelevant for the validation of the end point.

We retrospectively validated the primary end point by comparison with the course of the predefined individual HAE symptoms of pain, nausea, vomiting, cramps, and diarrhea associated with abdominal attacks. The symptom intensity was assessed by the patients as none, mild, moderate, or severe (*i.e.*, 0, 1, 2, or 3 for the calculation of the sum of symptom intensity scores) for up to 24 hours after the start of treatment at the same time points as the general symptom relief. Validation end points were (1) the time to the *first* decrease in intensity of any symptom present at baseline, (2) the time to the first decrease of the *sum* of intensity scores for all symptoms present at baseline, and (3) the first decrease in intensity of the *last* symptom present at baseline. The time to decrease in intensity of the first, the sum of all, or the last symptom was defined as the first time point with a decrease that persisted for at least two consecutive time points.

Statistical Analysis

The efficacy analyses for abdominal attacks in the I.M.P.A.C.T.1 study were based on the intention-to-treat principle and included all patients who received any blind study treatment and had an abdominal attack. The patients were analyzed according to the treatment group to which they were randomized.

Spearman rank correlation was used for correlation of the primary end point with the three validation end points. The primary end point and the validation end points were evaluated using the Wilcoxon one-sided two-sample test for the comparison of the C1-INH, 20 U/kg, group versus placebo. In addition, Hodges-Lehman estimates were used to estimate the treatment

effect. The analysis without imputation of rescue medication was the primary analysis for the end point validation.

RESULTS

Study Population

A total of 125 patients were randomized in the I.M.P.A.C.T.1 study.¹⁰ The treatment groups were similar in terms of sex, age, and race or ethnic group. Most patients (108) had type I HAE. Overall, 98 patients experienced abdominal attacks and 25 patients experienced facial attacks. The percentage of patients who received rescue study medication was considerably higher with placebo (57%) than with C1-INH, 10 U/kg (33%) or 20 U/kg (19%).

For the retrospective end point validation, only the 98 patients with abdominal attacks were further analyzed, because predefined individual symptoms associated with abdominal attacks (*i.e.*, pain, nausea, vomiting, cramps, and diarrhea) were evaluated by the patients. Thirty-three patients in the placebo group, 31 patients in the C1-INH, 10 U/kg group, group, and 34 patients in the C1-INH, 20 U/kg, group were treated for abdominal attacks. Most of the patients reported abdominal pain, cramps, and nausea at baseline, and the symptoms at baseline were mostly moderate or severe in intensity (see Fig. 1).

Study Outcomes

Construct validity was evaluated by correlation analysis of the validation end points with the primary end point. The validation end point time to first reduction of intensity of the last symptom present at baseline showed the highest correlation with the primary end point ($r = 0.77$; Table 1). Considerably lower correlations were found for the other two validation end points ($r = 0.60$ for the time to first reduction of intensity of a symptom; $r = 0.63$ for the time to first reduction in sum of symptom intensity scores). The correlation coefficients were similar for the analysis with imputation of rescue medication ($r = 0.81$ for the time to decrease in intensity of the last symptom; $r = 0.65$ for the time to first decrease in intensity of a symptom; $r = 0.68$ for the time to first reduction in sum of symptom intensity scores).

The primary end point (*i.e.*, time to onset of symptom relief) and the validation end points ([1] time to first decrease in intensity of any symptom, [2] time to decrease of the sum of intensity scores for all symptoms, and [3] time to decrease in intensity of the last symptom) were generally longest in the placebo group or the C1-INH, 10 U/kg group, and shortest in the C1-INH, 20 U/kg, group (Table 1). Because only the dose of C1-INH, 20 U/kg, had a significantly shorter time to onset of symptom relief compared with placebo in the

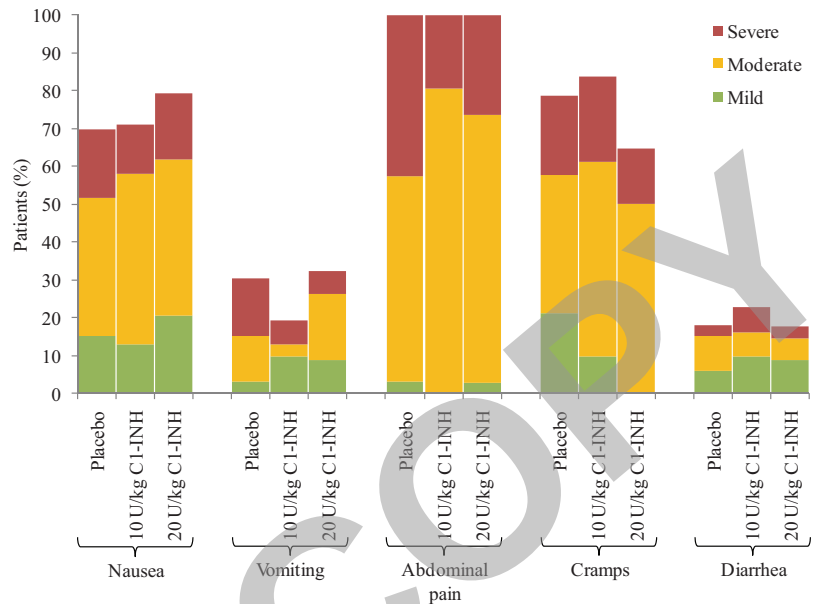


Figure 1. Clinical symptoms associated with abdominal attacks at baseline and intensity of symptoms (intention-to-treat population). There were no statistically significant differences in symptom intensity at baseline between treatment groups for any of the symptoms associated with abdominal attacks (two-sided Wilcoxon test, $\alpha = 0.05$).

I.M.P.A.C.T.1 study,¹⁰ a further comparison of the primary end point with the validation end points was performed only for the C1-INH, 20 U/kg, group.

With C1-INH, 20 U/kg, the largest differences compared with placebo were observed for the primary end point, *i.e.*, the time to onset of symptom relief, and the time to first reduction in the intensity of the last symptom (Fig. 2). Significant differences from placebo treatment were observed for the median time to onset of symptom relief (0.5 hours versus 1.23 hours; $p = 0.009$) and the median time to decrease in intensity of the last symptom present at baseline (0.5 hours versus 1.58 hours, $p = 0.0036$; Table 1). Similarly, the estimated treatment effect showed significant improvements for the primary end point (by 0.44 hours) and the time to first reduction of intensity of the last symptom (by 0.58 hours). No statistically significant differences between the C1-INH, 20 U/kg, group and the placebo group were observed for the other two validation end points (time to first decrease in intensity of a symptom and time to first decrease of the sum of intensity scores for all symptoms). Results for the primary end point and the three validation end points were similar when analyzed with imputation of rescue medication, as done for the primary efficacy analysis in the I.M.P.A.C.T.1 study; statistically significant differences between the C1-INH, 20 U/kg, group and the placebo group were also observed only for the primary end point ($p = 0.0093$) and the time to decrease in intensity of the last symptom ($p = 0.0015$).

DISCUSSION

In this study, we retrospectively validated the end point time to onset of symptom relief, which was assessed as the primary efficacy end point in the

I.M.P.A.C.T.1 study,¹⁰ as an appropriate disease measure by correlation with the course of individual symptoms of abdominal HAE attacks (*i.e.*, nausea, vomiting, pain, cramps, and diarrhea) that had been evaluated prospectively during the study.

The onset of symptom relief was strongly correlated with the time to first reduction of intensity of the last symptom present at baseline ($r = 0.77$). Two other symptom characteristics, *i.e.*, the time to first reduction of symptom intensity and the time to first reduction of the sum of symptom intensity scores, were less correlated with the onset of symptom relief ($r = 0.60$ and $r = 0.63$, respectively).

Analysis of single acute abdominal attacks showed that the median time to onset of symptom relief was significantly shorter with a dose of 20 U/kg of C1-INH (0.5 hours) than with placebo (1.2 hours). Both the time to onset of general symptom relief and the time to first reduction of intensity of the last symptom were significantly shorter in the C1-INH, 20 U/kg, group compared with the placebo group ($p = 0.009$ and $p = 0.0036$, respectively). The time to first reduction of symptom intensity and the time to first reduction of the sum of symptom intensity scores did not show any significant difference between the placebo group and the C1-INH, 20 U/kg, group. It should be noted that the validation of the end point was based on the correlation analysis only. However, the results for the comparisons between treatment groups were consistent with the correlation analysis and thus further increase the confidence in the validity of the end point.

Reliability of the end point of time to onset of symptom relief could not be formally tested because the data did not lend themselves to an evaluation of

Table 1 Results of primary and validation analyses for abdominal attacks (intention-to-treat population)

Parameter	Median Time, hr (range)			p Value§	20 U/kg-Placebo		Correlation Coefficient*
	Placebo (n = 33)	10 U/kg of C1-INH (n = 31)	20 U/kg of C1-INH (n = 34)		Hodges-Lehman Estimate hr (95% CI)		
Primary end point#							
Time to onset of symptom relief	1.233 (0.20–5.13)	1.083 (0.17–6.47)	0.500 (0.17–5.22)	0.009	–0.442 (–1.1; –0.034)		
Validation end points#							
Time to first decrease in intensity of a symptom	0.467 (0.23–4.67)	0.500 (0.25–5.08)	0.500 (0.25–5.22)	0.173	–0.017 (–0.5; 0.017)		0.60 (p < 0.0001)
Time to decrease of the sum of intensity scores for all symptoms	0.625 (0.23–4.67)	0.500 (0.25–5.08)	0.500 (0.25–5.22)	0.109	–0.083 (–0.53; 0.017)		0.63 (p < 0.0001)
Time to decrease in intensity of the last symptom	1.583 (0.25–6.72)	1.617 (0.25–6.78)	0.508 (0.25–5.58)	0.0036	–0.583 (–1.7; –0.133)		0.77 (p < 0.0001)

*Spearman rank correlation with primary end point. All treatment groups were included.

#Time to onset of symptom relief as determined by the patients, i.e., without setting the time to 24 hr for patients who received rescue study medication or analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma after 4 hr.

§One-sided two-sample Wilcoxon test; primary analysis.

C1-INH = C1 esterase inhibitor; CI = confidence interval.

test-retest reliability, which is one of the limitations of this retrospective end point validation. Furthermore, a moderate correlation between the primary end point and the validation end points was to be expected given that they are not entirely independent of each other. However, validity of the primary end point was indicated by the high correlation with the time to first reduction in intensity of the last symptom present at baseline; this correlation was considerably higher compared with the other two validation end points.

The onset to symptom relief is widely used as a clinical end point in HAE treatment. Waytes *et al.*¹² assessed the overall symptoms with a severity score of 0–3 (0–4 for laryngeal edema) for HAE attacks after treatment with C1-INH concentrate (25 U/kg) or placebo. They reported that the mean time from the start of the treatment to the beginning of improvement was shorter for the C1-INH infusions than the placebo infusions (55 minutes versus 563 minutes; $p < 0.001$). In an intention-to-treat analysis of the same placebo-controlled study by Kunschak *et al.*,¹³ the primary end point for HAE attacks, the time to relief of symptoms, was almost twice as fast after administration of the C1-INH concentrate compared with placebo ($p = 0.007$). Other clinical studies also used the time to onset of symptom relief as the primary efficacy end point for the treatment of acute HAE attacks.^{14,17} Taken together, the time to onset of symptom relief is commonly used and various clinical studies with C1-INH concentrate using this end point showed the efficacy in treating acute HAE attacks,^{10,12–14} indicating that the time to onset of symptom relief is a robust efficacy end point. However, no validation of this end point by correlation with the course of associated individual HAE symptoms has been reported to date.

More recently, Vernon *et al.*¹¹ developed the treatment outcome score (a composite measure that evaluates symptom change in response to treatment, taking symptom severity into account) and the mean symptom complex severity score (an arithmetic mean of symptom severity) to systematically capture the severity and change of all symptoms of the different anatomic regions. The treatment outcome score was highly correlated with a global improvement measure (a single-item categorical response assessment of overall improvement in symptoms completed by the patients) at 4 and 24 hours after treatment ($r = 0.90$ and $r = 0.71$, respectively), while the mean symptom complex severity score was only moderately correlated with the global improvement measure at 4 and 24 hours ($r = -0.59$). In contrast to our study, Vernon *et al.*¹¹ combined five symptom complexes (head/neck, stomach/gastrointestinal, genital/buttocks, *etc.*) in the treatment outcome score and mean symptom complex severity score, while we focused on individual symptoms of

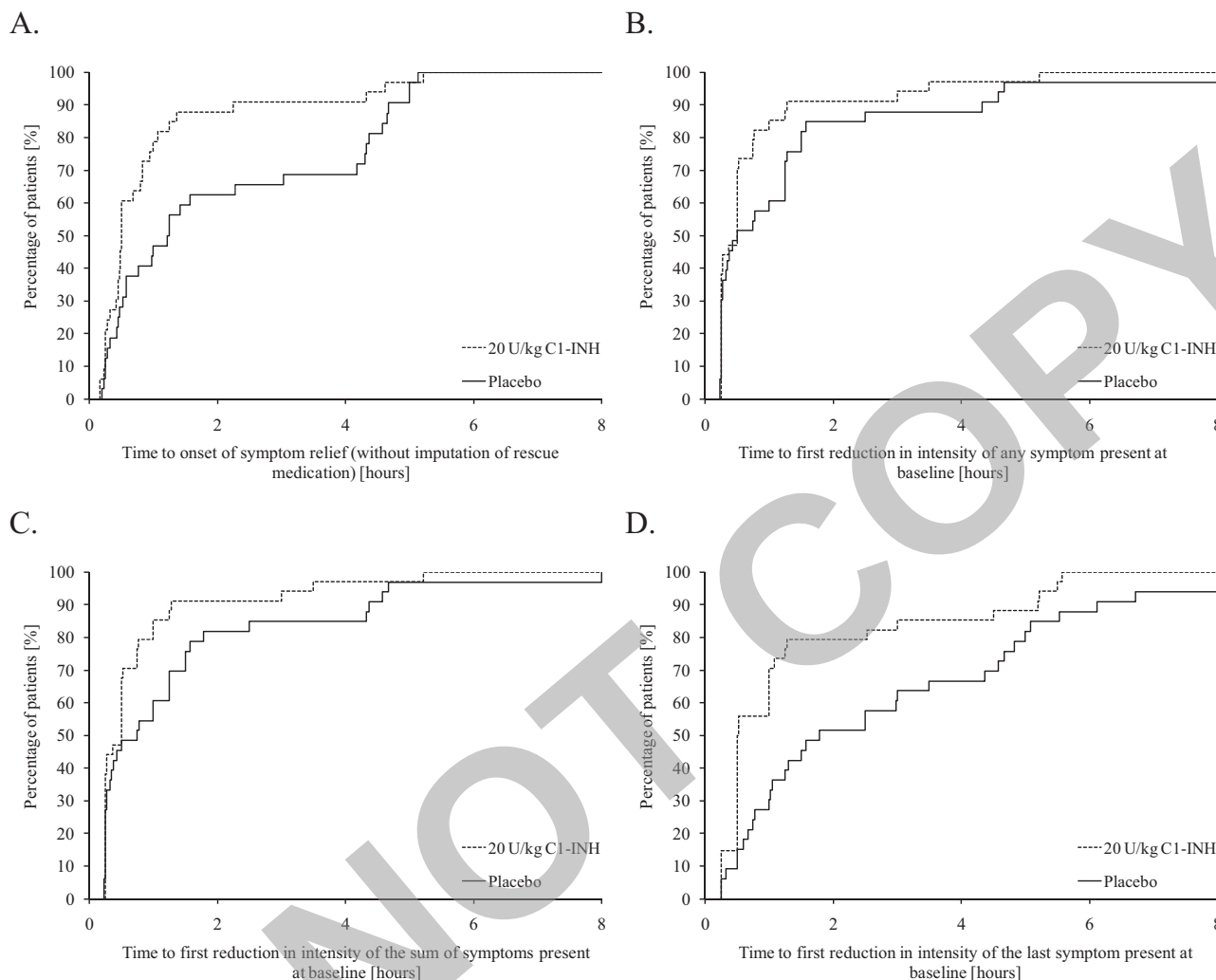


Figure 2. Kaplan-Meier curves for patients with abdominal attacks. (A) Time to onset of symptom relief (primary end point without imputation of rescue medication). (B) Time to first reduction in intensity of any symptom. (C) Time to first reduction in intensity of the sum of symptoms. (D) Time to first reduction in intensity of the last symptom present at baseline.

abdominal attacks for the comparison with the onset of overall symptom relief. However, the global improvement measure used by Vernon *et al.*¹¹ for comparison with their newly developed outcome measures, although evaluated only at 4 and 24 hours after the start of treatment, is somewhat similar to our primary end point, the time to onset of relief taking all symptoms into account. Both studies clearly indicate that patient-reported outcome measures are appropriate and accurate for the assessment of treatment effects in HAE.

In conclusion, the high correlation of the time to onset of relief with the time to first reduction of intensity of the last symptom and the statistically significant difference for these two parameters when comparing the C1-INH, 20 U/kg, treatment group with placebo show that the time to onset of relief, taking all symptoms into account, concurs with the time to onset of relief of the last symptom present at baseline and thus

is an appropriate and valid end point for assessing the efficacy of C1-INH treatment.

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