ORIGINAL ARTICLE

# Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor

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## ABSTRACT

### BACKGROUND

Hereditary angioedema is a disabling, potentially fatal condition caused by deficiency (type I) or dysfunction (type II) of the C1 inhibitor protein. In a phase 2 trial, the use of CSL830, a nanofiltered C1 inhibitor preparation that is suitable for subcutaneous injection, resulted in functional levels of C1 inhibitor activity that would be expected to provide effective prophylaxis of attacks.

### METHODS

We conducted an international, prospective, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase 3 trial to evaluate the efficacy and safety of self-administered subcutaneous CSL830 in patients with type I or type II hereditary angioedema who had had four or more attacks in a consecutive 2-month period within 3 months before screening. We randomly assigned the patients to one of four treatment sequences in a crossover design, each involving two 16-week treatment periods: either 40 IU or 60 IU of CSL830 per kilogram of body weight twice weekly followed by placebo, or vice versa. The primary efficacy end point was the number of attacks of angioedema. Secondary efficacy end points were the proportion of patients who had a response (≥50% reduction in the number of attacks with CSL830 as compared with placebo) and the number of times that rescue medication was used.

### RESULTS

Of the 90 patients who underwent randomization, 79 completed the trial. Both doses of CSL830, as compared with placebo, reduced the rate of attacks of hereditary angioedema (mean difference with 40 IU, −2.42 attacks per month; 95% confidence interval [CI], −3.38 to −1.46; and mean difference with 60 IU, −3.51 attacks per month; 95% CI, −4.21 to −2.81; P<0.001 for both comparisons). Response rates were 76% (95% CI, 62 to 87) in the 40-IU group and 90% (95% CI, 77 to 96) in the 60-IU group. The need for rescue medication was reduced from 5.55 uses per month in the placebo group to 1.13 uses per month in the 40-IU group and from 3.89 uses in the placebo group to 0.32 uses per month in the 60-IU group. Adverse events (most commonly mild and transient local site reactions) occurred in similar proportions of patients who received CSL830 and those who received placebo.

### CONCLUSIONS

In patients with hereditary angioedema, the prophylactic use of a subcutaneous C1 inhibitor twice weekly significantly reduced the frequency of acute attacks. (Funded by CSL Behring; COMPACT EudraCT number, 2013-000916-10, and ClinicalTrials.gov number, NCT01912456.)

HEREDITARY ANGIOEDEMA IS A DISabling and potentially fatal condition characterized by recurrent episodes of swelling without urticaria or pruritus. The condition is caused by deficiency (type I) or dysfunction (type II) of the C1 inhibitor protein.[1] Patients have insufficient C1 inhibitor function to prevent bradykinin production by the contact system, leading to episodes of increased capillary hyperpermeability and swelling. These episodes manifest clinically as angioedema attacks.[2,3]

Low levels of C1 inhibitor protein antigen or low functional levels of C1 inhibitor activity, as well as low levels of complement C4, are diagnostic for hereditary angioedema, and baseline C1 inhibitor function has been reported to correlate with disease severity.[4] According to clinical observations, a sustained threshold level of approximately 40% functional C1 inhibitor activity has been reported to confer certain protection against recurrent attacks.[5,6]

Regular intravenous C1 inhibitor replacement is effective at reducing the frequency and severity of attacks and has an acceptable safety and side-effect profile. A double-blind, placebo-controlled, crossover trial involving 22 patients with frequent attacks showed a 50% reduction in the frequency and severity of attacks with the use of an intravenous C1 inhibitor at a dose of 1000 IU twice weekly.[7] However, because of the technical difficulties of regular venous access, risks with the use of indwelling venous catheters, and patient considerations,[8,9] the development of a C1 inhibitor concentrate suitable for regular subcutaneous administration is of interest.

A phase 2 trial showed that administration of CSL830 (CSL Behring), a low-volume, human plasma–derived, pasteurized, nanofiltered C1 inhibitor preparation that is suitable for subcutaneous injection, resulted in a dose-dependent and constant increase in trough plasma levels of functional C1 inhibitor activity above 40%,[10] a biochemical finding expected to provide effective prophylaxis of attacks.

We describe the results of the Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT), a phase 3 trial testing the hypothesis that a twice-weekly subcutaneous injection of CSL830, as compared with placebo, could reduce the frequency of attacks of hereditary angioedema in patients with frequent attacks.

## METHODS

### TRIAL OVERSIGHT

The trial was jointly designed by the sponsor (CSL Behring) and the steering committee. The protocol, available with the full text of this article at NEJM.org, was approved by the appropriate regulatory authorities and ethics committees or institutional review boards. All the patients provided written informed consent. An independent data and safety monitoring board regularly monitored trial safety and provided recommendations to the sponsor on safety-related trial conduct.

The investigators at each participating center collected the data, which were analyzed by the sponsor with input from the steering committee. The members of the steering committee had access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The manuscript was drafted by the first author and revised by all the authors. Medical writing assistance, which was paid for by CSL Behring, was provided by ApotheCom.

### PATIENTS

Eligible patients were 12 years of age or older and had a clinical and central laboratory diagnosis of type I or II hereditary angioedema (functional C1 inhibitor activity of <50% and C4 antigen level below the normal level). All the patients had had four or more attacks requiring immediate treatment or medical attention or causing clinically significant functional impairment over a 2-month period within 3 months before screening, as documented in the patient's medical records. Full inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

During the trial, the protocol was amended to include patients who were receiving oral medications for prophylaxis of angioedema attacks, if they had received a stable dose for 3 months before screening and planned to continue throughout the trial. Patients who had received an intravenous C1 inhibitor for routine prophylaxis within 3 months before screening were excluded.

## TRIAL DESIGN

COMPACT was an international, prospective, multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial. After screening, eligible patients entered a run-in period of up to 8 weeks. All the patients had a clinical diagnosis of hereditary angioedema that had been confirmed by means of central laboratory testing and had had at least two attacks during any consecutive 4-week period or at least one attack during the first 2 weeks of the run-in period. The patients were randomly assigned in a 1:1:1:1 ratio by means of an interactive-response system to receive CSL830 at a dose of 40 IU per kilogram of body weight during the first 16-week treatment period followed by placebo for the second 16-week treatment period or vice versa (i.e., placebo first and CSL830 second); or CSL830 at a dose of 60 IU per kilogram followed by placebo or vice versa (Fig. S1 in the Supplementary Appendix).

Patients who had 12 or more attacks in a consecutive 4-week period (excluding the first 4 weeks of each treatment period) could progress to the next treatment period or to trial completion at the investigator's discretion. An end-of-trial visit was scheduled 1 week after completion of the second treatment period or if a patient was withdrawn from the trial.

## TREATMENT

CSL830 or placebo was administered by the patient twice weekly in a double-blind crossover manner during each treatment period. Blinded trial medication was provided as a lyophilized powder to be reconstituted with sterile water for injection; the dose was rounded up to the nearest milliliter per 500 IU. To maintain the blinding by varying the volume of the agent that each patient received during the two 16-week treatment periods, we provided a high-volume placebo (matching the volume of the 60-IU dose of CSL830) to patients who received the 40-IU dose of CSL830 and a low-volume placebo (matching the volume of the 40-IU dose of CSL830) to patients who received the 60-IU dose of CSL830.

Patients were trained to administer the injections at home. Injections were to be given by means of a manual slow-push method in a single site in the abdominal area, unless the investigator thought an alternative subcutaneous injection site was clinically more appropriate. Patients were permitted to use intravenous C1 inhibitor concentrate, icatibant, ecallantide, or fresh-frozen plasma as a rescue medication for on-demand treatment of attacks at any time during the trial or for preprocedural prophylaxis.

## CLINICAL ASSESSMENTS

Patients used an electronic diary on a daily basis to record symptoms, use of the trial drug, and any rescue therapy. The investigator reviewed the electronic diary at each trial visit and reported the details of the attack on the electronic case-report form. Functional C1 inhibitor activity and C1 inhibitor and C4 protein levels were measured, and clinical laboratory assessments were conducted throughout the trial at specified trial visits (see the trial protocol).

## OUTCOME MEASURES

The primary efficacy end point was the number of attacks of angioedema, as reported by the investigator. Secondary efficacy end points were the percentage of patients who had a response (≥50% reduction vs. placebo in the number of attacks) and the number of times that rescue medication was used. Exploratory end points included the number of days of angioedema symptoms, severity of attacks, and proportion of patients in whom the number of attacks was reduced to less than one attack per 4-week period from one attack or more per 4-week period with placebo. The numbers of attacks and uses of rescue medication were normalized for the number of days that the patient received the corresponding treatment.

Safety and the side-effect profile were monitored throughout the trial. Adverse events, serious adverse events, solicited local site reactions (including discomfort, swelling, bruising, or itching at the injection site), the presence of inhibitory anti–C1 inhibitor antibodies, results of viral serologic tests, and clinically significant abnormalities in laboratory assessments were assessed. In addition, a prespecified pharmacokinetic and pharmacodynamic analysis that was based on an interval-censored repeated time-to-event model was constructed to directly relate functional C1 inhibitor activity to the attack of angioedema.

## STATISTICAL ANALYSIS

All efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. Efficacy data were included from the beginning of week 3 for each treatment period to account for a run-in or washout period. The primary efficacy analysis was conducted without imputation for missing data. Safety analyses were based on the safety population, which included all the patients in the intention-to-treat population who had received at least one dose of a study drug.

We estimated that a sample size of 72 patients would provide a power of 80% to detect a relative difference in the primary end point of 30% between the two doses of CSL830 and a power of 99% to detect a difference between active treatment and placebo at an alpha level of 0.05, assuming that patients in the placebo group would have a mean number of 0.152 attacks per day. We estimated that 100 patients would need to undergo screening on the assumption that 20% of the patients would be ineligible to enter the treatment periods after the run-in period and that 10% of the patients who entered the treatment periods would withdraw before trial completion.

Descriptive statistics were used. For the comparison of the number of attacks and the number of times that rescue medication was used, normalized for the number of days that the patient received the corresponding treatment, a least-squares mean difference was estimated with 95% confidence intervals and P values with the use of a mixed-model accounting for the within-patient correlation. Hypothesis testing was performed hierarchically to preserve the preset level of significance of 0.05. Thus, we first tested the 60-IU dose of CSL830 versus low-volume placebo, and only if the null hypothesis was rejected at an alpha level of 0.05 did we test the 40-IU dose versus high-volume placebo. Testing of the 60-IU dose versus the 40-IU dose was considered to be exploratory and was always tested at an alpha level of 0.05 for informational purposes. All statistical tests were two-sided. Statistical analyses were conducted with the use of SAS software, version 9.1.3 (SAS Institute).

## RESULTS

### PATIENTS

The trial was conducted from December 2013 through October 2015. Overall, 115 patients were screened at 38 centers: 18 in the United States and 20 across Australia, Canada, the Czech Republic, Hungary, Israel, Italy, Romania, Spain, and the United Kingdom (Fig. S2 in the Supplementary Appendix). Of the 90 patients who underwent randomization, 11 discontinued for various reasons (Table S2 in the Supplementary Appendix).

Demographic and baseline clinical characteristics of the patients are shown in Table 1. In the 3 months before screening, 36% of the patients who received 40 IU of CSL830 per kilogram and 49% of those who received 60 IU per kilogram had received a prophylactic treatment to prevent attacks of angioedema. One of these patients continued to receive oral prophylaxis (danazol) during the trial. The mean (±SD) number of attacks per month during the run-in period, normalized for the number of days that the patient received the corresponding drug or placebo, was 4.6±2.2 for the 40-IU treatment sequences and 4.0±2.0 for the 60-IU treatment sequences. The mean duration of exposure was similar for all treatments: 16.3±1.6 weeks for 40 IU, 16.0±2.1 weeks for 60 IU, and 15.3±3.3 weeks for combined placebo.

### EFFICACY RESULTS

Among patients who received CSL830, the rate of attacks of angioedema was lower than the rate among patients who received placebo. The mean difference, as compared with placebo, was −2.42 attacks per month (95% confidence interval [CI], −3.38 to −1.46) with 40 IU and −3.51 attacks per month (95% CI, −4.21 to −2.81) with 60 IU (P<0.001 for both comparisons) (Table 2). No significant difference was seen between the 40-IU and 60-IU treatment sequences. The occurrence of symptoms and the use of rescue medication in each patient during each treatment period are shown in Figure S3 in the Supplementary Appendix.

Secondary and exploratory end points are also listed in Table 2. In patients with data that could be evaluated at both doses, the median reduction in the normalized number of attacks versus placebo was 88.6% (interquartile range, 69.6 to 100.0) with 40 IU of CSL830 and 95.1% (interquartile range, 79.0 to 100.0) with 60 IU. The percentage of patients who had a response was 76% in the 40-IU group and 90% in the 60-IU group. Overall, 43% of the patients in the 40-IU group and 58% of those in the 60-IU group had

**Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.***

| Characteristic | CSL830 Dose Groups | | Total CSL830 (N = 90) |
| --- | --- | --- | --- |
| | 40 IU (N = 45) | 60 IU (N = 45) | |
| Age — yr | 42.4±14.4 | 36.8±14.9 | 39.6±14.9 |
| Female sex — no. (%) | 28 (62) | 32 (71) | 60 (67) |
| Body weight — kg | 83.0±23.0 | 80.2±24.6 | 81.6±23.7 |
| Body-mass index† | 29.5±7.3 | 27.7±6.8 | 28.6±7.1 |
| Race — no. (%)‡ | | | |
| White | 40 (89) | 44 (98) | 84 (93) |
| Black | 3 (7) | 1 (2) | 4 (4) |
| Asian | 1 (2) | 0 | 1 (1) |
| Other | 1 (2) | 0 | 1 (1) |
| History of hereditary angioedema — no. (%) | | | |
| Type I | 41 (91) | 37 (82) | 78 (87) |
| Type II | 4 (9) | 8 (18) | 12 (13) |
| No. of attacks of angioedema in 3 mo before screening | 10.8±6.7 | 8.8±6.4 | 9.8±6.6 |
| Use of prophylaxis against attacks of hereditary angio-edema in 3 mo before screening — no. (%) | 16 (36) | 22 (49) | 38 (42) |
| Plasma-derived C1 inhibitor | 9 (20) | 14 (31) | 23 (26) |
| Oral prophylaxis | 8 (18) | 11 (24) | 19 (21) |
| Danazol | 6 (13) | 10 (22) | 16 (18) |
| Stanozolol | 2 (4) | 0 | 2 (2) |
| Oxandrolone | 0 | 1 (2) | 1 (1) |

* Plus–minus values are means ±SD. There were no significant differences at baseline between the treatment sequences in the characteristics shown. Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the patient.

at least a 90% reduction in attacks, and 53% of the patients in the 40-IU group and 71% of those in the 60-IU group had less than one attack per month. Overall, 38% of the patients in the 40-IU group and 40% of those in the 60-IU group did not have an attack, as compared with 9% and no patients, respectively, who received placebo. Patients in the 60-IU group had half as many attacks as those in the 40-IU group.

The average severity of attacks was lower in the patients who received CSL830 than in those who received placebo (Fig. 1). Thirteen patients who received CSL830 had a total of 52 severe attacks, and 64 patients who received placebo had a total of 252 severe attacks. In line with the observed reduction in the number of attacks regardless of their location in the body, the number of patients who had laryngeal attacks was reduced with CSL830, with 5 patients in the 40-IU

group, no patients in the 60-IU group, and 25 patients in the placebo group.

The mean normalized number of times that rescue medication was used was reduced with both doses of CSL830 versus placebo (Table 2). The rate of use of rescue medication was 71.7% lower among the patients in the 60-IU group than among those in the 40-IU group. In the 60-IU treatment sequences, the rate of use of rescue medication was lower than the rate of attacks.

At screening, the levels of functional C1 inhibitor activity, C1 inhibitor protein, and C4 protein were similar across the three groups; after randomization, all three biomarkers showed a dose-dependent increase that reached steady state at week 3 (Fig. S4A, S4B, and S4C in the Supplementary Appendix). In the population-based exposure-response analysis, an inverse relationship

**Table 2. Primary, Secondary, and Exploratory Efficacy End Points in the Intention-to-Treat Population.***

| End Point | Treatment Sequences with 40 IU/kg | | | | Treatment Sequences with 60 IU/kg | | | |
|---|---|---|---|---|---|---|---|---|
| | CSL830 (N=43) | Placebo (N=44) | Within-Patient Difference | P Value | CSL830 (N=43) | Placebo (N=42) | Within-Patient Difference | P Value |
| **Primary efficacy end point** | | | | | | | | |
| No. of time-normalized attacks per mo — mean (95% CI)†‡ | 1.19 (0.54 to 1.85) | 3.61 (2.96 to 4.26) | −2.42 (−3.38 to −1.46) | <0.001 | 0.52 (0.00 to 1.04) | 4.03 (3.51 to 4.55) | −3.51 (−4.21 to −2.81) | <0.001 |
| Reduction in attacks vs. placebo — %§ | | | | | | | | |
| Median | 89 | | | | 95 | | | |
| Mean | 55 | | | | 84 | | | |
| **Secondary efficacy end points** | | | | | | | | |
| Patients with a response — % (95% CI) | | | | | | | | |
| ≥50% reduction in attacks vs. placebo | 76 (62 to 87) | | | | 90 (77 to 96) | | | |
| ≥70% reduction in attacks vs. placebo | 67 (52 to 79) | | | | 83 (68 to 91) | | | |
| ≥90% reduction in attacks vs. placebo | 43 (29 to 58) | | | | 58 (42 to 72) | | | |
| Use of rescue medication per mo — mean (95% CI)†¶ | 1.13 (−1.44 to 3.69) | 5.55 (3.10 to 8.00) | −4.42 (−8.03 to −0.81) | 0.02 | 0.32 (−0.33 to 0.97) | 3.89 (3.23 to 4.55) | −3.57 (−4.50 to −2.64) | <0.001 |
| Reduction in use of rescue medication vs. placebo — % | | | | | | | | |
| Median | 89 | | | | 100 | | | |
| Mean | 70 | | | | 89 | | | |
| **Exploratory efficacy end points** | | | | | | | | |
| No. of days of hereditary angioedema symptoms per mo | 1.57±2.64 | 7.00±5.75 | | | 1.61±4.39 | 7.51±5.59 | | |
| Average severity score for attacks‖ | 1.77±0.59 | 2.03±0.49 | | | 1.64±0.56 | 1.94±0.47 | | |
| Patients with reduction to <1 attack per 4-wk period — no./total no. (%)** | 24/45 (53) | | | | 32/45 (71) | | | |

* Listed are values for the patients in the intention-to-treat population for whom data were available. CI denotes confidence interval.
† Values in this category are least-squares means as estimated from a mixed model.
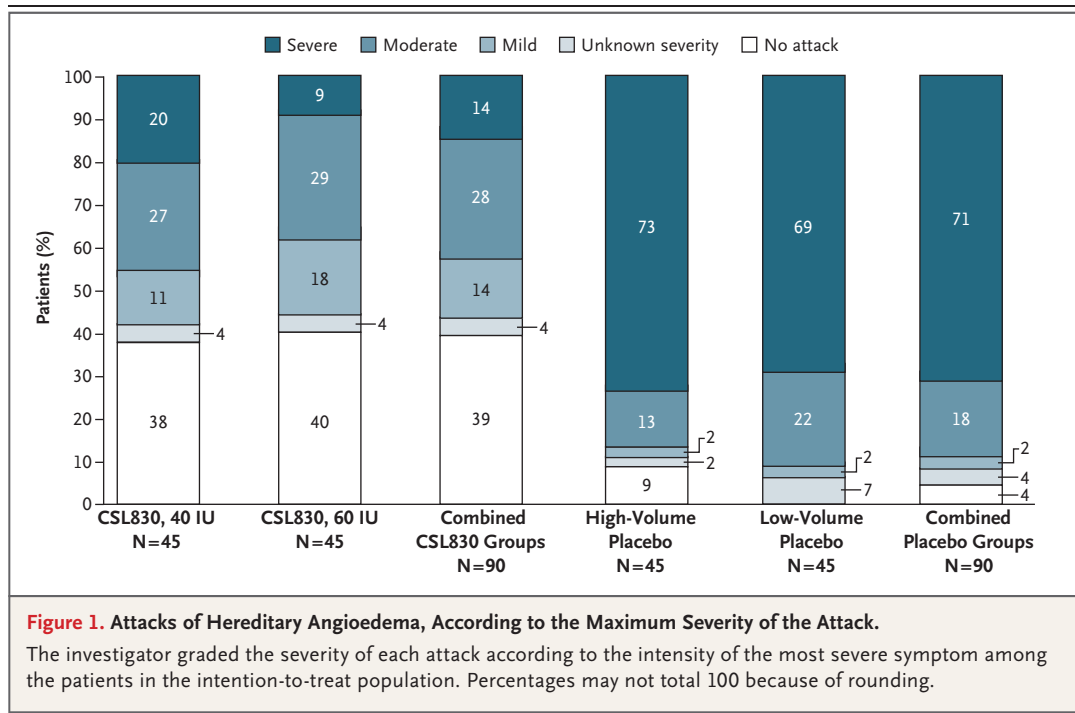‡ In this category, the estimated difference between the patients who received 40 IU of CSL830 per kilogram and those who received 60 IU of CSL830 per kilogram was −0.64; 95% CI, −1.43 to 0.16; P=0.11.
§ The reduction in attacks was evaluated in 38 patients in the 40-IU group and in 40 patients in the 60-IU group.
¶ In this category, the estimated difference between the patients who received 40 IU of CSL830 per kilogram and those who received 60 IU of CSL830 per kilogram was −0.76; 95% CI, −2.25 to 0.72; P=0.31.
‖ Severity scores were 1 for mild, 2 for moderate, and 3 for severe.
** Values are for patients who had at least one attack during a 4-week period while receiving placebo.

**Figure 1. Attacks of Hereditary Angioedema, According to the Maximum Severity of the Attack.**

The investigator graded the severity of each attack according to the intensity of the most severe symptom among the patients in the intention-to-treat population. Percentages may not total 100 because of rounding.

between the predicted functional C1 inhibitor activity at the time of an attack and the relative risk of an attack was established (Fig. 2).

### SAFETY AND SIDE EFFECTS

Adverse events were reported by similar proportions of patients in the CSL830 groups and the placebo groups (Table 3). The majority of reported adverse events were mild (in 95% of the patients in the 40-IU group, 76% of those in the 60-IU group, and 83% of those in the combined placebo group) and were reported by the investigators to be resolved by the end of the trial (98% of the patients in the 40-IU group, 94% of those in the 60-IU group, and 96% of those in the combined placebo group). Three adverse events led to trial discontinuation: pulmonary embolism in a patient who received placebo, urticaria in a patient who received 60 IU of CSL830, and an increase in liver aminotransferase levels in a patient who received 60 IU of CSL830) (Table S2 in the Supplementary Appendix). Four serious adverse events were reported in three patients: one event (urosepsis) in a patient who received the 40-IU dose and three events (pulmonary embolism, attack of angioedema, and syncope) in patients who received placebo.
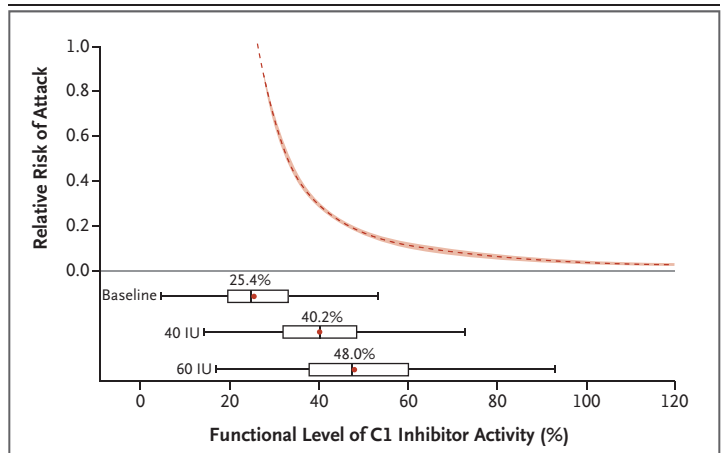
Most reported adverse events were injection-



**Figure 2. Relationship between Functional Levels of C1 Inhibitor Activity and the Relative Risk of an Attack of Hereditary Angioedema.**

The relative risk was expressed as the risk in relation to the baseline risk before treatment among patients with an observed geometric mean baseline functional level of C1 inhibitor activity of approximately 25%. The red dashed line indicates the median of the model-based risk relationship; the surrounding shaded area indicates the prediction intervals (standard errors). The box plots indicate the range of observed baseline and predicted functional levels of C1 inhibitor activity at steady-state troughs after the administration of CSL830 at doses of 40 IU per kilogram and of 60 IU per kilogram. In each box plot, the red dot indicates the geometric mean, the vertical line inside the box the median, the left and right sides of the box the lower and upper quartiles, and the I bars the minimum and maximum values.

**Table 3. Adverse Events Reported during the Trial.***

| Event | CSL830 Dose Groups | | Total CSL830 (N=86) | Placebo (N=86) |
|---|---|---|---|---|
| | 40 IU (N=43) | 60 IU (N=43) | | |
| | *number of patients (percent)* | | | |
| Any adverse event | 29 (67) | 30 (70) | 59 (69) | 57 (66) |
| Any related adverse event† | 14 (33) | 15 (35) | 29 (34) | 22 (26) |
| Any serious adverse event | 1 (2) | 0 | 1 (1) | 2 (2) |
| Any related serious adverse event† | 0 | 0 | 0 | 1 (1) |
| Adverse event leading to trial discontinuation | 0 | 2 (5) | 2 (2) | 1 (1) |
| Nonserious adverse event in ≥5% of patients | | | | |
| Injection-site reaction‡ | 12 (28) | 15 (35) | 27 (31) | 21 (24) |
| Nasopharyngitis | 1 (2) | 8 (19) | 9 (11) | 6 (7) |
| Upper-respiratory-tract infection | 3 (7) | 3 (7) | 6 (7) | 6 (7) |
| Hypersensitivity§ | 2 (5) | 3 (7) | 5 (6) | 1 (1) |
| Dizziness | 4 (9) | 0 | 4 (5) | 1 (1) |
| Fatigue | 1 (2) | 1 (2) | 2 (2) | 6 (7) |
| Back pain | 1 (2) | 1 (2) | 2 (2) | 5 (6) |

\* The safety analysis included all the patients in the intention-to-treat population who had received at least one dose of a study drug. Included are adverse events that had an onset within 24 hours after administration, which were followed until they resolved.
† Related adverse events were adverse events that were classified by the investigator as being related to CSL830.
‡ Injection-site reactions included bruising, erythema, pain, swelling, edema, hemorrhage, and induration.
§ Hypersensitivity included pruritus, rash, and urticaria.

site reactions, which occurred in 31% of the patients who received CSL830 and in 24% of those who received placebo. Of the injection-site reactions, 95% in the CSL830 groups and 95% in the placebo groups were mild; 83% in the CSL830 groups and 90% in the placebo groups resolved within 1 day after onset.

No seroconversions for the human immunodeficiency virus or hepatitis B or C virus were observed during the trial; such testing was performed as a safeguard since CSL830 is a plasma-derived product. No anaphylactic reactions or inhibitory anti–C1 inhibitor antibodies were detected.

## DISCUSSION

In COMPACT, among patients with hereditary angioedema, we found that twice-weekly administration of CSL830 at doses of 40 IU per kilogram or 60 IU per kilogram provided an excellent and dose-dependent preventive effect, as evidenced across multiple trial end points. The median reduction in the attack rate relative to placebo was 89% with 40 IU and 95% with 60 IU in patients who had data that could be evaluated during the two 16-week treatment periods. This treatment effect was associated with an overall reduced need for rescue medication.

C1 inhibitor replacement for prophylaxis is currently approved only as intravenous therapy. Its use was first described in two case reports in 1989.[11] On the basis of a placebo-controlled study[7] and some open-label studies,[12-15] international guidelines recommend twice-weekly intravenous infusions of a C1 inhibitor preparation (1000 IU) for routine prophylaxis.[8,16-18]

A previous randomized, controlled trial involving 22 patients showed the efficacy of an intravenous C1 inhibitor infusion regimen in preventing attacks of angioedema.[7] This trial showed a response rate (defined as ≥50% reduction in the frequency of attacks) of 50%.[19] With the use of similar criteria, a response rate of 76 to 90% was observed in our trial.

A recent study showed that patients who re-

ceived twice-weekly intravenous C1 inhibitor prophylaxis had breakthrough attacks that tended to occur shortly before the next scheduled infusion.[15] These findings suggest that low trough levels of functional C1 inhibitor predispose a patient to an increased risk of an attack. When modeled pharmacokinetic profiles of intravenous and subcutaneous C1 inhibitor were compared,[10] the simulated profiles of functional C1 inhibitor activity showed a lower peak-to-trough ratio and more consistent, sustained, and higher trough values after subcutaneous administration than after intravenous administration. Therefore, the better treatment response rate with a subcutaneous C1 inhibitor may be related to a sustained increase in C1 inhibitor activity to a level that is closer to physiologic values. On the basis of the pharmacokinetic and pharmacodynamic modeling, an inverse relationship between the relative risk of an attack and functional C1 inhibitor activity was established (Fig. 2). This finding suggests that if the C1 inhibitor activity level could be maintained closer to the lower limit of normal, the risk of an attack would approach zero. Data are lacking on the usefulness of individualized administration of C1 inhibitor replacement therapy to reach and maintain this target level.

The requirement for long-term, intravenous access with C1 inhibitor prophylaxis is a major clinical challenge, and despite expert advice to the contrary, subcutaneous ports are used, which can be associated with various medical complications.[9] A subcutaneous C1 inhibitor may help to overcome many of these disadvantages.

Our trial had a limited observation period of 14 weeks per treatment period (after the exclusion of the 2-week run-in or washout period). Therefore, it was not possible to assess the safety and preventive effects of long-term continuous prophylaxis with CSL830. A qualitative analysis is under way to explore reasons for the variability in patient responses. An open-label extension trial (ClinicalTrials.gov number, NCT02316353) is also ongoing to address this question and to investigate whether individual dose adjustments can further improve treatment response. This question was not addressed in the current trial.

In conclusion, we found that CSL830 significantly lowered the rate of hereditary angioedema attacks, as compared with placebo. More than 50% of the patients had no moderate-to-severe attacks while they were receiving CSL830.

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## APPENDIX

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