

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

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ABSTRACT

BACKGROUND

Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring hemostasis. In a phase 3, multicenter trial, we investigated its use as prophylaxis in persons who have hemophilia A without factor VIII inhibitors.

METHODS

We randomly assigned, in a 2:2:1 ratio, participants 12 years of age or older who had been receiving episodic treatment with factor VIII to receive a subcutaneous maintenance dose of emicizumab of 1.5 mg per kilogram of body weight per week (group A) or 3.0 mg per kilogram every 2 weeks (group B) or no prophylaxis (group C). The primary end point was the difference in rates of treated bleeding (group A vs. group C and group B vs. group C). Participants who had been receiving factor VIII prophylaxis received emicizumab at a maintenance dose of 1.5 mg per kilogram per week (group D); intraindividual comparisons were performed in those who had participated in a noninterventional study.

RESULTS

A total of 152 participants were enrolled. The annualized bleeding rate was 1.5 events (95% confidence interval [CI], 0.9 to 2.5) in group A and 1.3 events (95% CI, 0.8 to 2.3) in group B, as compared with 38.2 events (95% CI, 22.9 to 63.8) in group C; thus, the rate was 96% lower in group A and 97% lower in group B ($P < 0.001$ for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events, as compared with those in group C, who all had treated bleeding events. In the intraindividual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis ($P < 0.001$). The most frequent adverse event was low-grade injection-site reaction. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors.

CONCLUSIONS

Emicizumab prophylaxis administered subcutaneously once weekly or every 2 weeks led to a significantly lower bleeding rate than no prophylaxis among persons with hemophilia A without inhibitors; more than half the participants who received prophylaxis had no treated bleeding events. In an intraindividual comparison, emicizumab therapy led to a significantly lower bleeding rate than previous factor VIII prophylaxis. (Funded by F. Hoffmann–La Roche and Chugai Pharmaceutical; HAVEN 3 ClinicalTrials.gov number, NCT02847637.)

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REGULAR PROPHYLACTIC INTRAVENOUS infusion of factor VIII is the current treatment for persons with severe hemophilia A.¹⁻⁴ However, because of the half-life of factor VIII, more than two infusions per week are necessary for maintaining protective trough levels,⁵ which results in a substantial treatment burden^{6,7} and an unsatisfactory level of care for persons who are unable to adhere to this strategy. Despite regular prophylaxis, clinical and subclinical bleeding events may occur.⁸ Thus, treatments with a high efficacy and reduced burden are needed.

Emicizumab (Hemlibra, F. Hoffmann–La Roche), a recombinant, humanized, bispecific monoclonal antibody, bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring hemostasis.⁹⁻¹¹ The efficacy of once-weekly emicizumab therapy has been shown in persons who have hemophilia A with neutralizing anti-factor VIII alloantibodies (inhibitors).¹²⁻¹⁴ In a phase 3 trial (HAVEN 3), we assessed the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis in persons who have hemophilia A without inhibitors.

METHODS

OVERSIGHT

We initiated this phase 3, open-label, multicenter, randomized trial in September 2016. The trial was designed by the sponsors (F. Hoffmann–La Roche and Chugai Pharmaceutical) and the investigators. The data analysis was conducted by three authors (the trial statisticians and pharmacologist), who were employed by the sponsor and who vouch for accuracy and completeness of the data and analyses. The authors directed the development of the manuscript by Envision Pharma Group (funded by F. Hoffmann–La Roche) and critically reviewed subsequent drafts. Data were available to all the authors, who confirm adherence of the trial to the protocol (available with the full text of this article at NEJM.org) and the statistical analysis plan (see the Supplementary Appendix, available at NEJM.org).

The trial was conducted in compliance with the International Conference on Harmonisation guidelines for Good Clinical Practice¹⁵ and the principles of the Declaration of Helsinki.¹⁶ The protocol was approved by the institutional review board or ethics committee at each participating

center (see the Supplementary Appendix). An independent data and safety monitoring committee, which included three hemophilia experts, reviewed the safety of the trial. All the participants or their legally authorized representatives provided written informed consent before trial participation, and adolescents (12 to 17 years of age) provided written informed assent. The data-cutoff date for the analyses included in this article was September 15, 2017.

PARTICIPANTS

Eligible participants were 12 years of age or older with severe congenital hemophilia A (endogenous factor VIII activity, <1%), without current factor VIII inhibitors (<0.6 Bethesda units per milliliter), who were receiving episodic or prophylactic factor VIII infusions. Additional eligibility criteria are listed in the Methods section in the Supplementary Appendix.

DESIGN

Emicizumab prophylaxis was administered subcutaneously. Two maintenance regimens were evaluated to investigate whether flexible dosing frequency could be offered in the future; each regimen was predicted to provide effective bleeding control over the entire dosing period.¹⁷ Emicizumab prophylactic regimens included four initial loading doses of 3.0 mg per kilogram of body weight per week, followed by a dose of either 1.5 mg per kilogram per week or 3.0 mg per kilogram every 2 weeks (Fig. S1 in the Supplementary Appendix).

Participants receiving previous episodic therapy with factor VIII were randomly assigned in a 2:2:1 ratio to receive emicizumab once weekly (group A) or every 2 weeks (group B) or to receive no prophylaxis (group C). Randomization was conducted centrally by means of an interactive voice–Web–response system and was stratified according to the number of bleeding events (<9 or ≥9) that had occurred in the preceding 24 weeks. Participants who had been receiving adequate prophylactic factor VIII, as determined by the investigator, were assigned to receive once-weekly emicizumab (group D) and could continue factor VIII prophylaxis until the second loading dose of emicizumab, because the first loading dose results in plasma concentrations with measurable hemostatic benefit.¹⁸ At least 40 participants were required to complete 24 weeks



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or more of observation in a noninterventional study (ClinicalTrials.gov number, NCT02476942)¹⁹ before they could be enrolled in group D.

Additional factor VIII was administered at investigator-determined doses for breakthrough bleeding events. After 24 weeks or longer, participants in group C could switch to receiving emicizumab every 2 weeks (and remain in group C). All the participants could continue emicizumab therapy at or after 24 weeks. Using an electronic handheld device, participants regularly attested whether they had a bleeding event, and they recorded information about bleeding events and the administration of factor or emicizumab as soon as the events occurred. The collection of information regarding bleeding events and medications for hemophilia and the definitions of bleeding events have been described previously.¹³

The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) was administered every 12 weeks. Scores are on a scale from 0 to 100, with higher scores reflecting greater impairment,²⁰ and a change in the physical health subscale score of 10 points or more is considered to be clinically meaningful.²¹ Titers of factor VIII inhibitor were measured centrally with the use of a chromogenic Bethesda assay, and titers of 0.6 Bethesda units or more per milliliter were considered to be positive.^{22,23} Full details are provided in the Methods section in the Supplementary Appendix.

END POINTS

The primary end point was the difference (expressed as a ratio) in the rate of treated bleeding events (hereafter referred to as the bleeding rate) over a period of at least 24 weeks between randomly assigned groups of participants (group A vs. group C and group B vs. group C). The primary analysis occurred after the last randomly assigned participant and at least 40 participants from group D had completed 24 weeks in the trial or had withdrawn, whichever occurred first.

Secondary end points for the randomized comparisons, adjusted for multiple testing, included all bleeding events (treated and not treated), spontaneous and joint bleeding events, and the score on the Haem-A-QoL physical health subscale. In group D, analyses (adjusted for multiple testing) included intraindividual comparisons of bleeding rates. Intraindividual comparisons included only the participants who had been in the

noninterventional study, which allowed for analyses of similar, prospectively collected data regarding bleeding events and medication in a cohort of participants who had received factor VIII prophylaxis and emicizumab.

Target joints were defined as major joints (e.g., hip, elbow, wrist, shoulder, knee, and ankle) in which at least three bleeding events occurred over a 24-week period. At trial entry, the presence of target joints according to bleeding events in the 24 weeks before enrollment was recorded (see the Methods section in the Supplementary Appendix).

An exploratory efficacy end point was the preference for emicizumab prophylaxis or previous treatment according to a survey (EmiPref) that was completed at week 17 in groups A, B, and D. Safety end points were adverse events, serious adverse events, thromboembolic events, thrombotic microangiopathy, abnormal laboratory values, the development of antidrug antibodies, and the new development of factor VIII inhibitors. The pharmacokinetic objective was to characterize the trough plasma concentration of emicizumab according to the dosing regimen. Full details are provided in the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

On the basis of the evaluation of clinical considerations and the primary efficacy end point in a test for superiority, we estimated that a sample of 34 participants per randomized emicizumab group and 17 participants in the control group would provide the trial with a power of more than 90%, at a two-sided significance level of 0.05, to detect an effect size (i.e., the rate ratio of bleeding events in 1 year, defined as the rate in an emicizumab group divided by the rate in group C, which had received no prophylaxis) of $4 \div 14 = 0.29$ (null hypothesis: rate ratio = 1). The inclusion of 40 participants in group D was considered to be sufficient for the evaluation of the efficacy end point with precision on the basis of the width of the confidence interval for the estimated annualized bleeding rate.

For bleeding-related end points, comparisons of bleeding rate (which were calculated over the entire efficacy period) were performed with the use of a negative binomial-regression model. The model included the stratification factor (<9 or ≥9 bleeding events in the previous 24 weeks; see the

Supplementary Appendix) and accounted for various follow-up times to determine the bleeding rate per day, which was converted to an annualized bleeding rate. The intraindividual comparison (without stratification as a covariate) included the participant component in the model. The Haem-A-QoL scores were analyzed by means of analysis of variance (groups A vs. C and B vs. C, with baseline score and treatment by baseline interaction term included as covariates). The type I error for secondary end points was controlled with the use of a hierarchical testing framework, and the first two tests were the primary comparisons of group A with group C and of group B with group C (see the Supplementary Appendix).

The safety of emicizumab therapy was analyzed with the use of all the data collected during exposure to emicizumab (including in group C after the switch to emicizumab). Percentages (with 95% confidence intervals) of the participants who preferred emicizumab or their hemophilia treatment before enrollment, as recorded on the EmiPref survey, were calculated. Missing data that were related to the Haem-A-QoL and EmiPref assessments were considered to be missing completely at random, and no imputation was applied to the analyses (see the statistical analysis plan in the Supplementary Appendix).

RESULTS

TRIAL POPULATION

Overall, 152 participants were enrolled (Fig. 1, and Table S1 in the Supplementary Appendix), 1 of whom had undergone successful induction of immune tolerance. At enrollment, target joints were reported by 76 of 89 participants (85%) who had been receiving episodic therapy with factor VIII previously and by 26 of 63 (41%) who had been receiving prophylactic therapy with factor VIII previously.

EFFICACY

The annualized bleeding rate was 1.5 events (95% confidence interval [CI], 0.9 to 2.5) with the once-weekly emicizumab regimen (group A) and 1.3 events (95% CI, 0.8 to 2.3) with the regimen of emicizumab every 2 weeks (group B), as compared with 38.2 events (95% CI, 22.9 to 63.8) with no prophylaxis (group C). The bleeding rate was 96% lower in group A than in group C (rate ratio, 0.04; 95% CI, 0.02 to 0.08; $P < 0.001$)

Figure 1 (facing page). Disposition of the Participants in the Trial.

Participants who had been receiving episodic treatment with factor VIII were randomly assigned in a 2:2:1 ratio to group A, B, or C with the use of permuted blocks. Participants in group D (those who had received prophylactic factor VIII treatment previously) were enrolled without randomization. Of the 152 enrolled participants, 73 had been previously followed in the noninterventional study (NIS). Of these 73 participants, 25 who had received episodic treatment with factor VIII in the noninterventional study were randomly assigned to groups A, B, or C, and 48 who had been treated with factor VIII prophylaxis in the noninterventional study were assigned to group D. Participants in group C could receive emicizumab prophylaxis (and remain in group C) once they had completed at least 24 weeks of the trial while receiving no prophylaxis. In group A, the dose was increased to 3.0 mg per kilogram weekly in 1 participant after 24 weeks of follow-up. In group B, 1 participant discontinued treatment because of adverse events involving insomnia, alopecia, nightmare, lethargy, pruritus, headache, and depressed mood, all of which were considered by the investigator to be related to emicizumab. In group C, 1 participant was waiting to start emicizumab prophylaxis at the time of clinical cutoff. In group D, the dose was increased to 3.0 mg per kilogram weekly in 1 participant before 24 weeks of follow-up and in 3 participants after 24 weeks of follow-up.

and 97% lower in group B than in group C (rate ratio, 0.03; 95% CI, 0.02 to 0.07; $P < 0.001$) (Table 1). For each comparison, the results were consistent across the baseline characteristics that could be evaluated (Fig. S2 in the Supplementary Appendix).

No treated bleeding events were reported in 56% of the participants in group A and in 60% of those in group B, as compared with those in group C, who all had bleeding events (Table 1). The rates of all the secondary bleeding-related end points (spontaneous, joint, and target-joint bleeding events and all bleeding events) were lower with each emicizumab regimen than with no prophylaxis (Table 1). Among the 63 participants in group D, the annualized bleeding rate was 1.6 events (95% CI, 1.1 to 2.4), and 56% of the participants had zero bleeding events (Table S2 in the Supplementary Appendix). During emicizumab treatment, target joints were observed in 3 of 71 participants (4%) in groups A and B and in 2 of 63 (3%) in group D.

In an intraindividual comparison involving the 48 participants in group D who had participated in the noninterventional study, the annualized bleeding rate was 1.5 events (95% CI, 1.0 to 2.3)

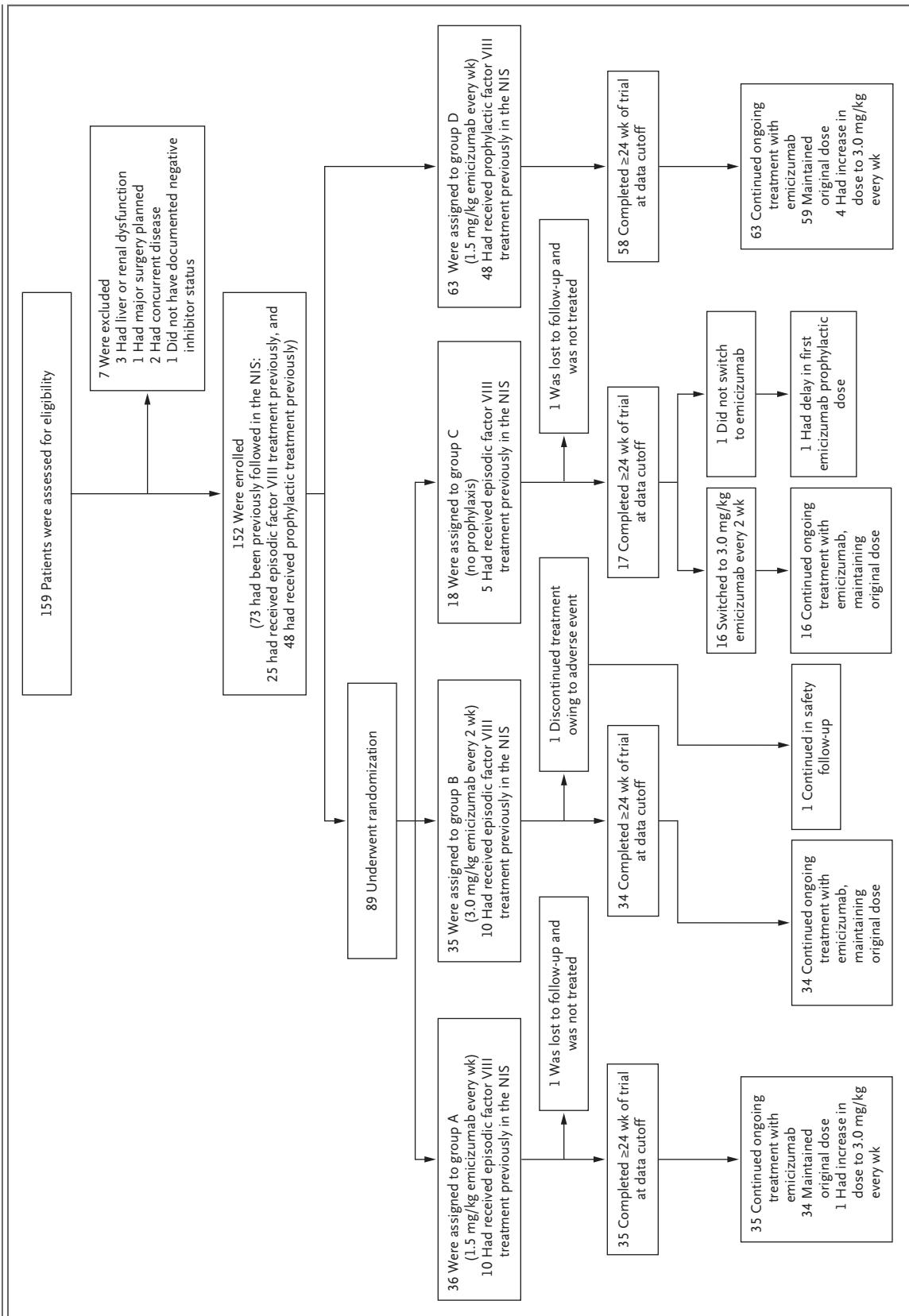


Table 1. Annualized Bleeding Rate among Participants Who Underwent Randomization and Had Received Episodic Factor VIII Treatment Previously.*

Variable	Group A: Emicizumab Once Weekly (N=36)	Group B: Emicizumab Every 2 Wk (N=35)	Group C: No Prophylaxis (N=18)
Median duration of efficacy period (range) — wk†	29.6 (17.3–49.6)	31.3 (7.3–50.6)	24.0 (14.4–25.0)
Bleeding events treated with factor VIII‡			
Annualized rate of bleeding events, model-based (95% CI)§	1.5 (0.9–2.5)	1.3 (0.8–2.3)	38.2 (22.9–63.8)
Rate ratio vs. control (95% CI)	0.04 (0.02–0.08)	0.03 (0.02–0.07)	—
Percent difference vs. control	–96	–97	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–2.5)	0.0 (0.0–1.9)	40.4 (25.3–56.7)
Percent of participants with 0 bleeding events (95% CI)	56 (38–72)	60 (42–76)	0 (0–18)
Percent of participants with 0–3 bleeding events (95% CI)	92 (78–98)	94 (81–99)	6 (<1–27)
All bleeding events, regardless of treatment with factor VIII			
Annualized rate of bleeding events, model-based (95% CI)§	2.5 (1.6–3.9)	2.6 (1.6–4.3)	47.6 (28.5–79.6)
Rate ratio vs. control (95% CI)	0.05 (0.03–0.10)	0.06 (0.03–0.10)	—
Percent difference vs. control	–95	–94	—
Median annualized rate of bleeding events (IQR)	0.6 (0.0–3.9)	1.6 (0.0–4.0)	46.9 (26.1–73.9)
Percent of participants with 0 bleeding events (95% CI)	50 (33–67)	40 (24–58)	0 (0–18)
Percent of participants with 0–3 bleeding events (95% CI)	86 (70–95)	86 (70–95)	6 (<1–27)
Treated events of spontaneous bleeding			
Annualized rate of bleeding events, model-based (95% CI)§	1.0 (0.5–1.9)	0.3 (0.1–0.8)	15.6 (7.6–31.9)
Rate ratio vs. control (95% CI)	0.06 (0.03–0.15)	0.02 (0.01–0.06)	—
Percent difference vs. control	–94	–98	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–1.3)	0.0 (0.0–0.0)	10.8 (2.1–25.9)
Percent of participants with 0 bleeding events (95% CI)	67 (49–81)	89 (73–97)	22 (6–48)
Percent of participants with 0–3 bleeding events (95% CI)	94 (81–99)	100 (90–100)	39 (17–64)
Treated events of joint bleeding			
Annualized rate of bleeding events, model-based (95% CI)§	1.1 (0.6–1.9)	0.9 (0.4–1.7)	26.5 (14.7–47.8)
Rate ratio vs. control (95% CI)	0.04 (0.02–0.09)	0.03 (0.02–0.07)	—
Percent difference vs. control	–96	–97	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–1.9)	0.0 (0.0–1.3)	21.3 (14.5–41.3)
Percent of participants with 0 bleeding events (95% CI)	58 (41–74)	74 (57–88)	0 (0–18)
Percent of participants with 0–3 bleeding events (95% CI)	94 (81–99)	97 (85–100)	17 (4–41)
Treated events of target-joint bleeding¶			
Annualized rate of bleeding events, model-based (95% CI)§	0.6 (0.3–1.4)	0.7 (0.3–1.6)	13.0 (5.2–32.3)
Rate ratio vs. control (95% CI)	0.05 (0.02–0.14)	0.05 (0.02–0.15)	—
Percent difference vs. control	–95	–95	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–1.4)	0.0 (0.0–0.0)	12.8 (0.0–39.1)
Percent of participants with 0 bleeding events (95% CI)	69 (52–84)	77 (60–90)	28 (10–54)
Percent of participants with 0–3 bleeding events (95% CI)	97 (86–100)	97 (85–100)	39 (17–64)

* Participants in groups A, B, and C had received episodic treatment with factor VIII previously. IQR denotes interquartile range.

† The start of the efficacy period for each participant was the first day with available data. The end of the efficacy period in groups A and B was the day of clinical cutoff or treatment discontinuation. The end of the efficacy period in group C was the day before the first dose of emicizumab or the day of discontinuation.

‡ The primary analysis occurred after the last randomly assigned participant and at least 40 participants from group D had completed 24 weeks in the trial or had withdrawn. Three participants who withdrew had a follow-up duration that was shorter than 24 weeks.

§ The annualized bleeding rate was calculated with the use of a negative binomial-regression model.

¶ Target joints were defined as major joints (e.g., hip, elbow, wrist, shoulder, knee, and ankle) in which at least three bleeding events occurred over the 24-week period before trial entry.

|| P<0.001 for the comparison with group C.

Table 2. Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group D), as Compared with Events in the Same Participants during Prophylactic Factor VIII Treatment Previously in the Noninterventional Study.*

Variable	Group D in Current Trial: Emicizumab Prophylaxis (N = 48)	Noninterventional Study: Factor VIII Prophylaxis (N = 48)
Median duration of efficacy period (range) — wk [†]	33.7 (20.1–48.6)	30.1 (5.0–45.1)
Annualized rate of bleeding events, model-based (95% CI) [‡]	1.5 (1.0–2.3)	4.8 (3.2–7.1)
Rate ratio vs. control (95% CI)	0.32 (0.20–0.51)	—
Percent difference vs. control	–68 [§]	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Percent of participants with 0 bleeding events (95% CI)	54 (39–69)	40 (26–55)
Percent of participants with 0–3 bleeding events (95% CI)	92 (80–98)	73 (58–85)

* Data are shown for 48 participants in group D who had participated in an earlier noninterventional study of factor VIII prophylaxis. In group D, these participants received emicizumab at a once-weekly dose of 1.5 mg per kilogram.

[†] The efficacy period for the noninterventional study group was defined as the time between the day of handheld-device activation and either the date of study withdrawal or completion, whichever occurred first.

[‡] The annualized bleeding rate was calculated with the use of a negative binomial-regression model.

[§] P<0.001 for the comparison with the noninterventional study.

with once-weekly emicizumab therapy, as compared with 4.8 events (95% CI, 3.2 to 7.1) during factor VIII prophylaxis, a result that indicated a 68% lower rate in favor of emicizumab prophylaxis (rate ratio, 0.32; 95% CI, 0.20 to 0.51; P<0.001) (Table 2). Of these 48 participants, 41 were eligible for inclusion in an analysis of adherence to factor VIII prophylaxis during the noninterventional study (see the Results section in the Supplementary Appendix). A total of 27 of 41 participants (66%) were administered at least 80% of the prescribed doses, whereas 14 (34%) reported receiving less than 80% of the doses. Among the 21 participants who had at least 80% adherence to both factor VIII–prescribed frequency and prescribed dose, the annualized bleeding rate was 4.3 events (95% CI, 1.2 to 10.7) and the median annualized bleeding rate was 1.8 events (interquartile range, 0.0 to 4.3), rates that were similar to the annualized bleeding rates among all 48 participants (Table 2). All the bleeding-related secondary end points in the hierarchical testing framework reached statistical significance.

HEALTH-RELATED QUALITY OF LIFE

The observed difference (adjusted mean) in the Haem-A-QoL physical health subscale score at week 25, as compared with group C, was 12.5 points (95% CI, –2.0 to 27.0) in group A (P=0.09) and 16.0 points (95% CI, 1.2, 30.8) in group B; the latter comparison was not considered to be significant owing to the order of end points in

the hierarchical testing framework. The EmiPref survey was completed by 95 of 134 eligible participants (71%). Of all the survey respondents, 94% (95% CI, 87 to 98) preferred emicizumab, and 45 of 46 participants (98%; 95% CI, 88 to 100) in group D favored emicizumab over factor VIII prophylaxis.

SAFETY

Overall, 543 adverse events were reported in 127 of 150 participants who received emicizumab. The most common adverse event was injection-site reaction (in 38 participants [25%]) (Table 3). One participant discontinued treatment owing to several low-grade adverse events that were considered by the investigator to be related to emicizumab. No deaths, thrombotic microangiopathy, or thrombotic events occurred. A total of 14 unique serious adverse events were reported. Of 215 events of co-exposure to emicizumab and factor VIII that occurred in 64 participants, 43 involved an average dose of factor VIII of at least 50 IU per kilogram per 24 hours, of which 8 events lasted 24 hours or longer (Table S3 in the Supplementary Appendix). No serious adverse events were related to co-exposure to emicizumab and factor VIII. The trial was not designed to characterize the factor VIII–induced hemostasis in participants receiving emicizumab.

No new factor VIII inhibitors developed in participants receiving emicizumab. Two participants who had negative results on the inhibitor assays

Table 3. Adverse Events in Participants Receiving Emicizumab Prophylaxis, According to Trial Group.

Variable	Group A: Emicizumab Once Weekly (N=36)	Group B: Emicizumab Every 2 Wk (N=35)	Group C: Emicizumab Every 2 Wk (N=16)*	Group D: Emicizumab Once Weekly (N=63)	Total (N=150)
Median duration of exposure period (range) — wk	29.3 (17.3–49.1)	30.1 (6.1–50.1)	7.1 (0.1–26.1)	33.1 (18.0–48.1)	29.0 (0.1–50.1)
No. of adverse events	143	145	19	236	543
Most common adverse events — no. of participants (%) †					
Injection-site reaction ‡	9 (25)	7 (20)	2 (12)	20 (32)	38 (25)
Upper respiratory tract infection	4 (11)	4 (11)	0	8 (13)	16 (11)
Nasopharyngitis	2 (6)	6 (17)	0	10 (16)	18 (12)
Arthralgia	7 (19)	6 (17)	1 (6)	14 (22)	28 (19)
Headache	3 (8)	4 (11)	1 (6)	8 (13)	16 (11)
Influenza	1 (3)	3 (9)	0	5 (8)	9 (6)
No. of serious adverse events §	1	3	0	10	14
Adverse event leading to discontinuation of treatment — no. of participants (%) ¶	0	1 (3)	0	0	1 (1)

* Data are for the period of emicizumab prophylaxis only. At the clinical cutoff date, one participant was lost to follow-up and another was waiting to start emicizumab therapy.

† Shown are events that occurred in at least 5% of all the participants who received emicizumab prophylaxis.

‡ The injection-site events were of grade 1 or 2.

§ Serious adverse events included a bleeding event (in four participants), cardiac disorder (in one), infection (in three), musculoskeletal disorder (in three), loosening of an orthopedic device (in one), psychiatric disorder (in one), and trauma (in one). An event of nephrolithiasis occurred in one participant after the dose was increased to 3 mg per kilogram per week. None of these events were considered by the investigator to be related to emicizumab treatment.

¶ One participant in group B discontinued treatment because of multiple low-grade adverse events (insomnia [grade 2], alopecia [grade 1], nightmare [grade 2], lethargy [grade 2], pruritus [grade 1], headache [grade 1], and depressed mood [grade 1]) that were considered by the investigator to be related to emicizumab.

that had been conducted at the local site to determine eligibility had detectable inhibitor in centrally tested baseline samples (3.7 and 3.1 Bethesda units per milliliter); titers declined spontaneously during the trial. Another participant had undergone induction of immune tolerance in 1987 and subsequently had intermittent detectable inhibitor. This participant had a detectable inhibitor titer at week 13 (1.6 Bethesda units per milliliter) that spontaneously declined at week 25 (0.7 Bethesda units per milliliter).

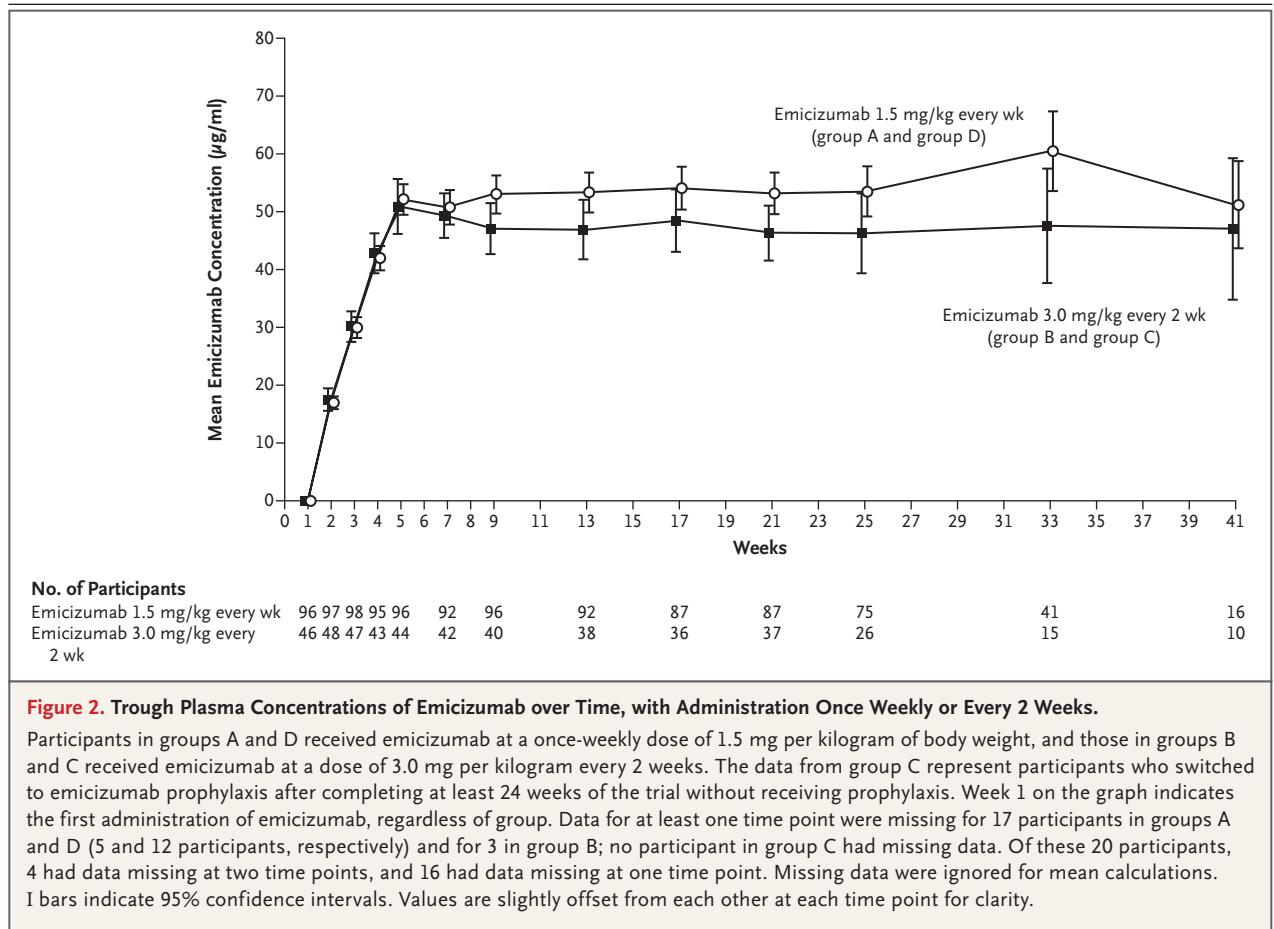
PHARMACOKINETICS AND IMMUNOGENICITY

Effective trough plasma concentrations of emicizumab were sustained with the two maintenance doses for the duration of the trial, a finding that is consistent with a half-life of approximately 30 days and with predictions that were based on an earlier study¹⁷ (Fig. 2). All the participants had sustained exposure to emicizumab, and no anti-drug antibodies were detected.

DISCUSSION

In the HAVEN 3 trial, subcutaneous emicizumab prophylaxis administered once weekly or every 2 weeks resulted in bleeding rates that were significantly lower by more than 95% than the rate with no prophylaxis. With each randomized emicizumab regimen, more than 55% of the participants had no treated bleeding events, and more than 90% of the participants had three or fewer events. Accordingly, we observed clinically meaningful lower rates of all bleeding events and of spontaneous, joint, and target-joint bleeding events, a finding that favored emicizumab therapy over no prophylaxis. This finding is further reflected by the observation that the percentage of participants who had a target joint after the initiation of emicizumab therapy was lower than the percentage at baseline.

The results of this trial are similar to data from the HAVEN 1 trial, which showed a bleed-



ing rate with emicizumab therapy that was 87% lower than the rate with no prophylaxis among adolescents or adults with inhibitors ($P < 0.001$).¹³ In the HAVEN 2 trial, 95% of children younger than 12 years of age had no treated bleeding events.¹⁴ Furthermore, in the HAVEN 1 trial, reductions in the bleeding rate were observed in subsequent 24-week periods beyond the initial 24-week observation period.²⁴

The intraindividual comparison showed the superiority of emicizumab therapy in the HAVEN 3 trial over the factor VIII prophylaxis that had been used in the noninterventional study, with a bleeding rate that was significantly lower by 68%. The robustness of these results stems from available prospectively collected and granular data regarding bleeding events and hemophilia medication from the two treatment periods, which had similar follow-up durations. Furthermore, identical definitions of bleeding events and methods were applied. The intraindividual comparison offers a robust design controlling for patient-related confounders that is particularly suitable for study-

ing rare, stable diseases (e.g., hemophilia) and interventions without carryover effect (e.g., factor VIII). The validity of the noninterventional study as a representative comparator is confirmed by the examination of bleeding rates relative to several prospective studies of factor VIII prophylaxis (Table S5 in the Supplementary Appendix). The observed median annualized bleeding rate of 1.8 events in the noninterventional study was consistent with rates that have been shown in other studies (range, 0.9 to 4.1 events). A total of 40% of the participants in the noninterventional study had no bleeding events, a finding that is consistent with the rates of 25.8 to 62.5% that have been reported in these pivotal studies of factor VIII prophylaxis, thereby confirming that the results of the noninterventional study are a representative comparator. Furthermore, the similar outcomes with factor VIII prophylaxis in the noninterventional study and phase 3 trials of factor VIII show empirically that the participants in the noninterventional study received appropriate prophylaxis.

Almost all the respondents to the treatment-preference survey favored emicizumab over their episodic or prophylactic factor VIII regimen that was in place before enrollment. Approximately 30% of the eligible participants did not complete the EmiPref survey because some sites were unaware of this separate assessment at week 17. Given the nature of the missing data, the analysis is unlikely to be affected by selection bias. This observation was corroborated by the fact that, after 24 weeks of treatment, all the participants elected to continue emicizumab therapy.

Emicizumab had a favorable safety profile with no unexpected safety signals. Co-exposure to factor VIII at doses of 50 IU or more per kilogram for 24 hours or longer was not associated with serious adverse events. Specifically, no thrombotic microangiopathy or thromboembolic complications occurred, and to date these events were observed only in the HAVEN 1 trial in participants with concomitant exposure to emicizumab and activated prothrombin complex concentrate.¹³ Owing to its higher affinity for activated factor IX and factor X,²⁵ activated factor VIII outcompetes emicizumab for binding to its targets, which results in nonadditive coagulation potential at high concentrations of factor VIII.²⁶ This situation is in contrast to the synergistic effect on thrombin generation with combinations of emicizumab and activated prothrombin complex concentrate.²⁷

Effective trough concentrations of emicizumab were sustained with each maintenance regimen throughout the trial. Despite slightly lower trough concentrations, maintenance dosing every 2 weeks was associated with efficacy similar to that with once-weekly dosing, as predicted.¹⁷

In conclusion, the administration of emicizumab once weekly or every 2 weeks was associated with significantly lower bleeding rates than the rate with no prophylaxis. In an intraindividual analysis, once-weekly emicizumab prophylaxis led to a bleeding rate that was significantly lower than the rate with previous factor VIII prophylaxis. The effect of emicizumab prophylaxis on bleeding rate, its mode and frequency of administration, and its safety profile are reflected in the participants' treatment preferences. In addition to the results from the phase 3 HAVEN trials,^{13,14,24,28} emerging data from early-phase studies of gene therapy with adeno-associated virus vectors in adults are encouraging.²⁹⁻³¹ Al-

though it is difficult to predict how the treatment approach will evolve, emicizumab therapy represents one option that holds promise to improve the care of patients with hemophilia A.

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APPENDIX

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