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Emicizumab Prophylaxis in Hemophilia A with Inhibitors

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ABSTRACT

BACKGROUND

Emicizumab (ACE910) bridges activated factor IX and factor X to restore the function of activated factor VIII, which is deficient in persons with hemophilia A. This phase 3, multicenter trial assessed once-weekly subcutaneous emicizumab prophylaxis in persons with hemophilia A with factor VIII inhibitors.

METHODS

We enrolled participants who were 12 years of age or older. Those who had previously received episodic treatment with bypassing agents were randomly assigned in a 2:1 ratio to emicizumab prophylaxis (group A) or no prophylaxis (group B). The primary end point was the difference in bleeding rates between group A and group B. Participants who had previously received prophylactic treatment with bypassing agents received emicizumab prophylaxis in group C.

RESULTS

A total of 109 male participants with hemophilia A with inhibitors were enrolled. The annualized bleeding rate was 2.9 events (95% confidence interval [CI], 1.7 to 5.0) among participants who were randomly assigned to emicizumab prophylaxis (group A, 35 participants) versus 23.3 events (95% CI, 12.3 to 43.9) among those assigned to no prophylaxis (group B, 18 participants), representing a significant difference of 87% in favor of emicizumab prophylaxis (P<0.001). A total of 22 participants in group A (63%) had zero bleeding events, as compared with 1 participant (6%) in group B. Among 24 participants in group C who had participated in a noninterventional study, emicizumab prophylaxis resulted in a bleeding rate that was significantly lower by 79% than the rate with previous bypassing-agent prophylaxis (P<0.001). Overall, 198 adverse events were reported in 103 participants receiving emicizumab prophylaxis; the most frequent events were injection-site reactions (in 15% of participants). Thrombotic microangiopathy and thrombosis were reported in 2 participants each (in the primary analysis) who had received multiple infusions of activated prothrombin complex concentrate for breakthrough bleeding. No antidrug antibodies were detected.

CONCLUSIONS

Emicizumab prophylaxis was associated with a significantly lower rate of bleeding events than no prophylaxis among participants with hemophilia A with inhibitors. (Funded by F. Hoffmann–La Roche and Chugai Pharmaceutical; HAVEN 1 ClinicalTrials.gov number, NCT02622321.)

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Hemophilia A is characterized by spontaneous or traumatic bleeding caused by deficient coagulation factor VIII activity.[1] The current standard of care for persons with hemophilia A with a severe bleeding phenotype is prophylactic intravenous infusions of factor VIII two to three times weekly; however, exposure to factor VIII concentrates is associated with the development of neutralizing anti–factor VIII alloantibodies (inhibitors), which render replacement factor VIII ineffective, in approximately 30% of patients with hemophilia A.[2] Inhibitors result in substantial medical complications and decreased health-related quality of life.[3-5] Treatments for hemophilia A in patients with a high titer of inhibitors (≥5 Bethesda units per milliliter) include eradication with induction of immune tolerance and episodic or prophylactic treatment with bypassing agents (recombinant activated factor VII [factor VIIa] or activated prothrombin complex concentrate).[2] The efficacy of bypassing agents remains suboptimal, and both options involve frequent intravenous infusions that depend on adequate venous access; thus, more effective and less burdensome treatments are needed.

Emicizumab (ACE910) is a recombinant, humanized, bispecific monoclonal antibody[6,7] that bridges activated factor IX and factor X to restore the function of missing activated factor VIII, which is needed for effective hemostasis. Owing to its unique structure, emicizumab is not expected to be affected by existing factor VIII inhibitors or to induce new development of such inhibitors. In a small phase 1 study, there were no dose-limiting toxic effects with once-weekly subcutaneous administration of emicizumab; this treatment markedly reduced the rate of bleeding episodes among participants with hemophilia A with or without inhibitors.[8]

The phase 3 HAVEN 1 trial assessed the efficacy, safety, and pharmacokinetics of once-weekly subcutaneous emicizumab prophylaxis in patients with hemophilia A with inhibitors. The primary objective was to compare bleeding rates among participants previously given episodic treatment with bypassing agents who received emicizumab prophylaxis versus no prophylaxis. In addition, to enable direct and accurate intraindividual comparisons of previous outcomes with bypassing agents with outcomes with emicizumab prophylaxis, a prospective, noninterventional study (ClinicalTrials.gov number, NCT02476942) was designed and conducted as part of the clinical development of emicizumab. The noninterventional study collected detailed, real-world data on bleeding events and safety outcomes from a cohort of patients with hemophilia A who received episodic or prophylactic treatment with bypassing agents according to local, routine clinical practice.[9] Participants in the noninterventional study were eligible to subsequently participate in the HAVEN 1 trial, provided that they met the eligibility criteria.

Methods

Trial Oversight

This phase 3, open-label, multicenter, randomized trial was initiated on November 17, 2015. A delay in trial registration (December 2, 2015) occurred owing to an unexpected issue in the internal tracking systems of the sponsor (F. Hoffmann–La Roche), which prevented an accurate assessment of the estimated timing of the enrollment of the first participant; one participant was enrolled before trial registration. The trial was designed by the sponsor, and data were collected by the participants and site investigators. Data analysis was conducted by the trial statistician and pharmacologist (both employed by the sponsor), who vouch for the completeness and accuracy of the data and analyses. Specific direction from the authors informed the development of the first draft of the manuscript by Envision Pharma Group (funded by F. Hoffmann–La Roche), and that draft was subsequently critically reviewed by the authors. All the authors had access to the data and confirm adherence to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org.

The trial was conducted at 43 centers (in 14 countries) in compliance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[10] and the principles of the Declaration of Helsinki.[11] The trial protocol was approved by the institutional review board or ethics committee at each participating center. All adult participants or legally authorized representatives provided written informed consent before trial participation, and adolescents (12 to 17 years of age) also provided written informed assent. The data cutoff date for the primary analysis and all the data points included in this article was October 25, 2016.

1. **This phase 3, open-label, multicenter, random- ized trial was initiated on November 17, 2015.**
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[Lindsey Wehrwein on behalf of Ginger Oppenheimer]

2. **The phase 3 HAVEN 1 trial assessed the efficacy, safety, and pharmacokinetics of once- weekly sub...**
Anchor Name: Oldenburg/p810/col1/para3/ln1-8 *[Ashley Finkelstein]*

TRIAL PARTICIPANTS

Eligible participants, including participants from the noninterventional study, were 12 years of age or older with congenital hemophilia A (of any severity), had a history of a high titer of factor VIII inhibitor (≥5 Bethesda units per milliliter), and were receiving episodic or prophylactic treatment with bypassing agents. Additional eligibility criteria are provided in the Methods section in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN

Participants receiving episodic treatment with bypassing agents before trial entry were randomly assigned in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis at a dose of 3.0 mg per kilogram of body weight weekly for 4 weeks, followed by 1.5 mg per kilogram weekly thereafter (group A), or to the control group (no emicizumab prophylaxis and, because the trial was open-label, no subcutaneous control injections; group B) (Figs. S1 and S2 in the Supplementary Appendix). Participants who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis in group C. Group D (also receiving emicizumab prophylaxis) comprised participants who were unable to enroll in HAVEN 1 groups A, B, or C before they were closed to enrollment. Participants who were randomly assigned to group B could receive emicizumab prophylaxis after completing at least 24 weeks in the trial (and remained in group B). All the participants receiving emicizumab were administered the same dose according to the same schedule and could receive episodic treatment with bypassing agents for breakthrough bleeding, as needed.

After at least 24 weeks of emicizumab prophylaxis, participants could continue taking maintenance therapy with 1.5 mg per kilogram weekly or, if they had had at least two spontaneous and clinically significant treated bleeding events in the past 24 weeks of emicizumab administration, both occurring after the end of the loading-dose period (termed "suboptimal control of bleeding"), start taking an increased dose of 3.0 mg per kilogram weekly. (For details on suboptimal control of bleeding, see the Methods section in the Supplementary Appendix.)

Definitions of bleeding events were adapted from the criteria of the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee.[12] A bleeding event was considered to be treated if it was directly followed by the administration of a hemophilia medication that was reported to be a treatment for bleeding. (For details on definitions, see the Methods section in the Supplementary Appendix.) Information on bleeding and medications was documented at the time of a bleeding event or medication use or at least once every 8 days. Assessment of health-related quality of life occurred every 4 weeks, and assessment of health status occurred at the time of a bleeding event and every 4 weeks.

END POINTS

The primary end point was the difference in the rate of treated bleeding events (hereafter referred to as the bleeding rate) over a period of at least 24 weeks between participants receiving emicizumab prophylaxis (group A) and those receiving no prophylaxis (group B) after the last randomly assigned participant had completed 24 weeks in the trial or had discontinued participation, whichever occurred first. Secondary end points for the randomized comparison (group A vs. group B) included additional bleeding-related end points (all bleeding events [both treated and not treated with bypassing agents] and events of spontaneous bleeding, joint bleeding, and target-joint bleeding), health-related quality of life (Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL] physical health subscale and total score at week 25), and health status (the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L] visual-analogue scale and index utility score at week 25). The Haem-A-QoL scales range from 0 to 100, with lower scores reflecting better health-related quality of life. Clinically meaningful differences are 10 points for the score on the physical health subscale and 7 points for the total score.[13] Scores on the EQ-5D-5L visual-analogue scale range from 0 to 100, and index utility scores range from −0.4 to 1.0; higher scores indicate better health status. Clinically meaningful differences are 7 and 0.07 points, respectively.[14,15] Additional bleeding-related end points included intraindividual comparisons of the bleeding rate and the rate of all bleeding events among participants in groups A and C who had participated in the noninterventional study.

Safety end points were adverse events, injection-site reactions, serious adverse events, thromboembolic events, abnormal laboratory values,

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and antidrug antibodies. The pharmacokinetic objective was to characterize emicizumab exposure over time. Exploratory biomarkers included those related to thrombosis (time profiles of D-dimer and prothrombin fragment 1.2).

STATISTICAL ANALYSIS

Calculation of the sample size (with the use of the Wald test) was based on the primary efficacy end point and clinical considerations. We estimated that a sample of 51 participants with a withdrawal rate of 10% in the control group would provide a power of more than 95% at a two-sided significance level of 0.05 to detect an effect size of 4/18=0.22 (null hypothesis: rate ratio=1). For all bleeding-related end points, comparisons of the bleeding rate in group A versus group B and the intraindividual comparisons were performed with the use of a negative binomial-regression model to determine the bleeding rate per day, which was converted to an annualized bleeding rate. End points with respect to health-related quality of life and health status were analyzed with the use of analysis of covariance. Type I error for secondary end points was controlled through the hierarchical testing framework. For all efficacy end points and corresponding safety analyses, only the no-prophylaxis period was included from group B. For end points with respect to intraindividual comparisons, only those who participated in the noninterventional study were included, to allow for analyses that used prospective data collection with the same detail for bleeding and medication data before and during emicizumab treatment. Additional analyses to allow for a comprehensive assessment of emicizumab efficacy and safety were conducted with the use of all the data collected during emicizumab prophylaxis.

RESULTS

TRIAL POPULATION

All 109 participants enrolled were male patients with hemophilia A with inhibitors, with a median age of 28 years (range, 12 to 75) (Table 1, and Table S1 in the Supplementary Appendix). Most had severe hemophilia; 7 of 109 participants previously had mild or moderate disease. Although participants who had previously received episodic or prophylactic treatment with bypassing agents could enroll in group D, at the time of data cutoff all 7 participants in group D had received episodic treatment with bypassing agents. The percentage of participants who had previously undergone induction of immune tolerance was as follows: 40% in group A, 39% in group B, 67% in group C, and 43% in group D. Most participants (70%) had target joints; 49% had more than one target joint. The median exposure to emicizumab treatment was 24.0 weeks (range, 3.0 to 47.9) overall and 29.5 weeks (range, 3.3 to 47.9) in group A (see the Results section in the Supplementary Appendix).

EFFICACY

The annualized bleeding rate was 2.9 events (95% confidence interval [CI], 1.7 to 5.0) with emicizumab prophylaxis (group A) versus 23.3 events (95% CI, 12.3 to 43.9) with no prophylaxis (group B), representing a significant difference of 87% in favor of emicizumab prophylaxis (P<0.001) (Fig. 1, and Table S2 in the Supplementary Appendix). Results were consistent across subgroups (Fig. S3 in the Supplementary Appendix). Significant differences in favor of emicizumab prophylaxis were also observed in all secondary bleeding-related end points, including events of spontaneous bleeding, joint bleeding, and target-joint bleeding as well as all bleeding events (Table S2 in the Supplementary Appendix). Of the 35 participants who were randomly assigned to emicizumab prophylaxis, 22 (63%) had zero bleeding events (median annualized bleeding rate, 0.0 events; interquartile range, 0.0 to 3.7) (Table S2 in the Supplementary Appendix). Only 1 of the 18 participants (6%) who were assigned to no prophylaxis had zero bleeding events.

Among 24 participants in group C who had participated in the noninterventional study, intraindividual comparisons showed a significantly lower bleeding rate with emicizumab prophylaxis than with previous bypassing-agent prophylaxis (annualized bleeding rate, 3.3 events [95% CI, 1.3 to 8.1] vs. 15.7 events [95% CI, 11.1 to 22.3]), representing a difference of 79% (P<0.001) (Fig. 2). Among 24 participants in group A who had participated in the noninterventional study, the bleeding rate was also significantly lower with emicizumab prophylaxis than with previous episodic treatment with bypassing agents (annualized bleeding rate, 1.7 events [95% CI, 0.7 to 4.1] vs. 21.6 events [95% CI, 15.4 to 30.2]), representing a difference of 92% (P<0.001) (Fig. S3 in the Supplementary Appendix).

For emicizumab prophylaxis as compared with

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Table 1. Demographic and Clinical Characteristics of the Participants.*

Characteristic	Group A: Emicizumab Prophylaxis (N=35)	Group B: No Prophylaxis (N=18)	Group C: Emicizumab Prophylaxis (N=49)	Group D: Emicizumab Prophylaxis (N=7)	Total (N=109)
Age					
Median — yr	38.0	35.5	17.0	26.0	28.0
Range — yr	12–68	13–65	12–75	19–49	12–75
<18 yr — no. (%)	4 (11)	2 (11)	26 (53)	0	32 (29)
Hemophilia severity at baseline — no. (%)					
Mild	2 (6)	0	1 (2)	0	3 (3)
Moderate	2 (6)	0	1 (2)	1 (14)	4 (4)
Severe	31 (89)	18 (100)	47 (96)	6 (86)	102 (94)
≥9 Bleeding events in 24 wk before trial entry — no. (%)	24 (69)	13 (72)	26 (53)	3 (43)	66 (61)
Target joints†					
Yes — no. (%)	25 (71)	13 (72)	34 (69)	4 (57)	76 (70)
>1 — no./total no. (%)	18/25 (72)	10/13 (77)	24/34 (71)	1/4 (25)	53/76 (70)
Highest historical titer of factor VIII inhibitor					
No. of participants with available data‡	32	16	47	6	101
Median — Bethesda units/ml	84.5	102.0	309.0	240.0	180.0
Range — Bethesda units/ml	5–1570	18–4500	11–5000	28–2125	5–5000
Previous induction of immune tolerance — no. (%)	14 (40)	7 (39)	33 (67)	3 (43)	57 (52)

* Participants who had received episodic treatment with bypassing agents before trial entry were randomly assigned in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis (group A) or no emicizumab prophylaxis (group B). Participants who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis in group C. Group D (also receiving emicizumab prophylaxis) comprised participants who were unable to enroll in groups A, B, or C before they were closed to enrollment. Participants who were randomly assigned to group B had the opportunity to receive emicizumab prophylaxis once they had completed at least 24 weeks in the trial (and remained in group B) (Figs. S1 and S2 in the Supplementary Appendix). Participants receiving emicizumab continued to receive episodic treatment with bypassing agents for breakthrough bleeding, as needed. Information on previous use of episodic and prophylactic coagulation products is available in Table S1 in the Supplementary Appendix.
† All values are based on electronic case-report forms and not on data from the noninterventional study.
‡ All participants with available data had a factor VIII inhibitor titer of at least 5 Bethesda units per milliliter.

no prophylaxis (group A vs. group B), the adjusted means of observed differences at week 25 and clinically meaningful differences as determined from published literature, respectively, were as follows: score on the Haem-A-QoL physical health subscale, 21.6 points (95% CI, 7.9 to 35.2; P=0.003) and 10 points; total score on the Haem-A-QoL, 14.0 points (95% CI, 5.6 to 22.4; P=0.002) and 7 points; score on the EQ-5D-5L visual-analogue scale, –9.7 points (95% CI, –17.6 to –1.8; P=0.02) and 7 points; and EQ-5D-5L index utility score, –0.16 points (95% CI, –0.25 to –0.07; P=0.001) and 0.07 points. The observed differences between the two groups indicate that emicizumab prophylaxis had significant benefits with respect to health-related quality of life and health status.

SAFETY

Overall, 198 adverse events were reported in 103 participants receiving emicizumab prophylaxis. The most frequently reported adverse events were injection-site reactions, with 28 events in 15 participants (15%) (Table 2). All were mild in intensity and resolved, except for 1 moderate event of injection-site hematoma, which occurred on trial day 2 and resolved on day 28. Proportionally fewer participants had adverse events in groups B and D than in groups A and C; however, observation periods were also shorter. Overall, 12 serious adverse events were reported in 9 participants (9%) (Table S3 in the Supplementary Appendix). Thrombotic microangiopathy (in 2 participants) and cavernous sinus thrombosis and skin necrosis–superficial throm-

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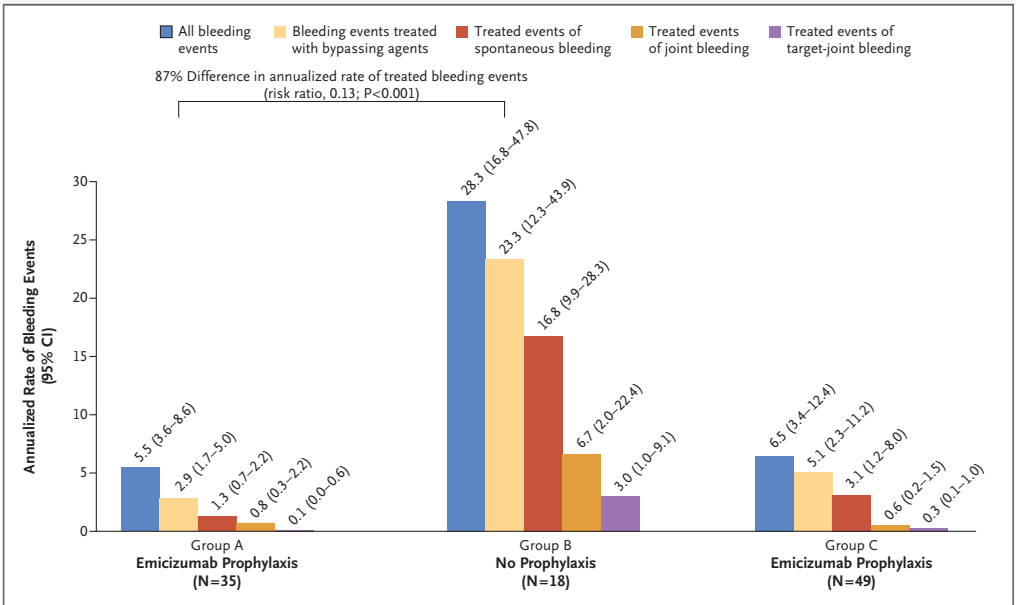

Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C.

The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.

bophlebitis (in 1 participant each) were reported in participants who had received multiple infusions of activated prothrombin complex concentrate while receiving emicizumab prophylaxis before event onset. (Case details are provided in the Results section in the Supplementary Appendix.) Both events of thrombotic microangiopathy resolved after treatment with activated prothrombin complex concentrate was stopped, and neither thrombotic event required anticoagulation. Two participants (1 with thrombotic microangiopathy and 1 with thrombosis) restarted emicizumab treatment.

After the data cutoff for the primary analysis, thrombotic microangiopathy developed in 1 additional participant 5 days after his previous emicizumab dose and after 4 consecutive days of treatment with activated prothrombin complex concentrate for rectal hemorrhage; the rectal bleeding was recurrent and eventually fatal. As assessed by the investigator, thrombotic microangiopathy was resolving at the time of death.

Of 104 participants who received emicizumab prophylaxis, 28 (27%) used activated prothrombin complex concentrate, 34 (33%) used recombinant factor VIIa, and 13 (12%) used both bypassing agents (Table S4 in the Supplementary Appendix). A range of doses of recombinant factor VIIa was used, although treatment episodes generally lasted for 1 day. Most use of activated prothrombin complex concentrate was less than 100 U per kilogram for 1 day, but a small number of treatment episodes averaged more than 100 U per kilogram daily and lasted more than 1 day (19 treatment events) (Table S5 in the Supplementary Appendix). The 5 participants who had thrombotic microangiopathy or thrombosis did so after treatment with activated prothrombin complex concentrate that averaged more than 100 U per kilogram daily for more

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[Lindsey Wehrwein on behalf of Ginger Oppenheimer]

3. **Anchor Name: Oldenburg/p814/col2/para2/ln1-5** *[Ashley Finkelstein]*

Participant No.	Bypassing-Agent Prophylaxis: Duration of efficacy period (days)	Bypassing-Agent Prophylaxis: No. of events	Emicizumab Prophylaxis: Duration of efficacy period (days)	Emicizumab Prophylaxis: No. of events
1	313	39	85	9
2	239	6	48	3
3	127	11	175	8
4	133	1	286	4
5	113	2	224	3
6	210	6	245	2
7	131	7	246	1
8	106	0	317	0
9	77	0	296	0
10	57	0	295	0
11	84	4	282	0
12	189	7	259	0
13	272	31	240	0
14	187	7	226	0
15	253	5	224	0
16	240	3	198	0
17	243	21	181	0
18	240	5	140	0
19	322	7	118	0
20	219	3	98	0
21	345	16	93	0
22	231	28	90	0
23	313	12	58	0
24	240	19	44	0

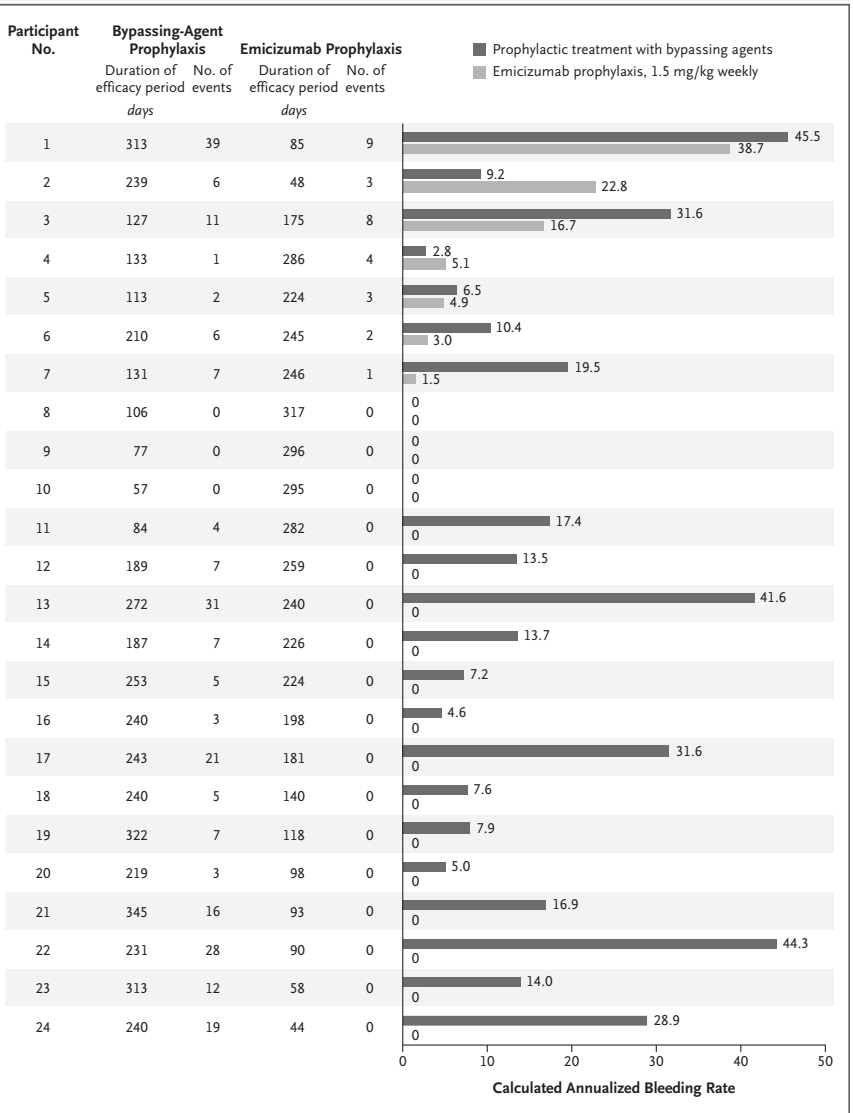

Figure 2. Intraindividual Comparison of Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group C) versus Previous Prophylactic Treatment with Bypassing Agents before Trial Entry.

Shown are data for the 24 participants in group C who had participated in the noninterventional study. Data are sorted according to the annualized bleeding rate with emicizumab prophylaxis in descending order and then according to descending duration of efficacy period with regard to emicizumab prophylaxis.

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Table 2. Adverse Events in Participants Receiving Emicizumab Prophylaxis, According to Trial Group.*

Event	Group A (N=34)	Group B (N=13)†	Group C (N=49)	Group D (N=7)	Total (N=103)
	number of participants (percent)				
Injection-site reaction	8 (24)	1 (8)	5 (10)	1 (14)	15 (15)
Headache	3 (9)	1 (8)	6 (12)	2 (29)	12 (12)
Fatigue	3 (9)	1 (8)	2 (4)	0	6 (6)
Upper respiratory tract infection	7 (21)	0	2 (4)	0	9 (9)
Arthralgia	2 (6)	1 (8)	3 (6)	0	6 (6)

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

than 1 day (see the Results section in the Supplementary Appendix). No events occurred after the use of activated prothrombin complex for 1 day, after treatment with recombinant factor VIIa alone (even at high doses), or with emicizumab prophylaxis alone. Levels of D-dimer and prothrombin fragment 1.2 were not affected by emicizumab treatment over time.

PHARMACOKINETIC AND IMMUNOGENICITY VARIABLES

Mean trough plasma concentrations of emicizumab of more than 50 μg per milliliter were observed after four loading doses of 3.0 mg per kilogram weekly and sustained throughout the trial with maintenance doses of 1.5 mg per kilogram weekly (Fig. 3). No participants tested positive for antidrug antibodies; however, two participants had pharmacokinetic profiles with declining exposure to emicizumab that were potentially indicative of antidrug antibodies (Fig. S7 in the Supplementary Appendix). After 24 weeks of emicizumab treatment, factor VIII inhibitor titers remained stable or tended to decline over time in the majority of participants.

DISCUSSION

In the HAVEN 1 trial, once-weekly emicizumab prophylaxis that was administered subcutaneously in patients with hemophilia A with inhibitors was associated with a bleeding rate that was 87% lower than the rate with no prophylaxis. These findings were supported by substantially lower rates of other bleeding-related end points (events of spontaneous bleeding, joint bleeding, and target-joint bleeding as well as all bleeding events) with emicizumab prophylaxis than with no prophylaxis. A total of 63% of the participants who were randomly assigned to receive emicizumab prophylaxis had zero bleeding events during the trial. These positive outcomes confirm previously reported results of a phase 1 study.[8] The events of thrombotic microangiopathy and thrombosis that developed in five participants during the trial were associated with the use of high cumulative doses of activated prothrombin complex concentrate for breakthrough bleeding during the receipt of emicizumab prophylaxis.

A prospective intraindividual comparison showed that emicizumab prophylaxis resulted in a bleeding rate that was 79% lower than the rate observed with previous bypassing-agent prophylaxis. The markedly lower rate of bleeding events with emicizumab prophylaxis than with no prophylaxis translated into significant benefits in participants' health-related quality of life and health status.[13-15]

The events of thrombotic microangiopathy and thrombosis that were observed developed after treatment with activated prothrombin complex concentrate at doses averaging more than 100 U per kilogram daily for more than 1 day during the administration of emicizumab prophylaxis; no events were reported with emicizumab prophylaxis either alone or with activated prothrombin complex concentrate administered for only 1 day or with recombinant factor VIIa (administered without activated prothrombin complex concentrate). In addition, no elevations in the level of D-dimer or prothrombin fragment 1.2 over time were observed, which suggests no significantly increased risk of thromboembolism

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[Lindsey Wehrwein on behalf of Ginger Oppenheimer]

in association with emicizumab prophylaxis alone. Two events of thrombotic microangiopathy resolved completely (the third participant died from rectal hemorrhage after the primary analysis), and the thrombotic events did not require anticoagulation. Recovery from these events occurred in the continued presence of emicizumab in plasma owing to its long half-life,[16] and no recurrence of thrombotic microangiopathy or thrombosis was seen in the two participants who restarted emicizumab.

Synergistic thrombin generation has previously been shown with activated prothrombin complex concentrate in combination with emicizumab in vitro and in vivo.[17] Substrates for emicizumab to form the intrinsic tenase complex are supplied by activated prothrombin complex concentrate, along with other activated and nonactivated coagulation factors that have half-lives of up to 60 hours and can accumulate with multiple doses.[18] Although the data are scant, the combined use of activated prothrombin complex concentrate and emicizumab prophylaxis appears to be associated with a substantial risk of toxic effects, which may limit the usefulness of this bypassing agent in patients who bleed while receiving emicizumab prophylaxis.

No antidrug antibodies were detected; however, two participants had pharmacokinetic profiles with declining emicizumab concentrations over time that were potentially indicative of antidrug antibodies. One participant had no bleeding events while receiving emicizumab prophylaxis, and the other is being monitored after an increase in the dose of emicizumab, which occurred shortly before the primary analysis. Both participants remained in the trial; longer follow-up will provide further insight into the efficacy and pharmacokinetic outcomes of these participants.

Stable trough plasma concentrations of emicizumab were observed after 4 weeks of loading doses and were sustained with weekly maintenance doses throughout the trial. With this previously untested dosing regimen, which was determined by means of pharmacokinetic and pharmacodynamic modeling, the trough concentrations that were observed (>50 μg per milliliter) are expected to result in a bleeding rate of zero among at least 50% of the participants.[19]

Limitations of the trial include its open-label nature, which may have affected the results for end points with respect to health-related quality of life and health status; however, because all results for primary and secondary end points were positive, these consistent results probably reflect true differences between the randomly assigned groups. Selection bias for groups C and D should also be considered. At the time of enrollment, participants had had at least six and two bleeding events during the previous 24 weeks of prophylactic and episodic treatment with bypassing agents, respectively. Thus, these participants could potentially show a more substantial decrease in bleeding events over the course of the trial than participants with lower pretrial bleeding rates, had they been eligible. Finally, follow-up for some participants (in groups C and D) was less than 24 weeks; however, all randomly assigned participants had at least 24 weeks of follow-up for the primary and secondary end points, and durable efficacy has been shown for up to 2 years in the phase 1 study.[20]

In conclusion, emicizumab prophylaxis was associated with a significantly lower rate of bleeding events than no prophylaxis or previous prophylactic treatment with bypassing agents among patients with hemophilia A with inhibitors, and it improved health-related quality of life. Emicizumab was safe when administered alone or in conjunction with recombinant factor VIIa

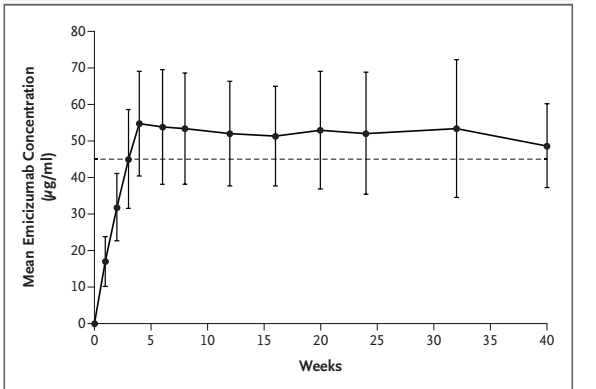

Figure 3. Observed Trough Plasma Concentrations of Emicizumab over Time with Once-Weekly Dosing (102 Patients).

As determined by pharmacokinetic and pharmacodynamic modeling, emicizumab doses of 1.5 mg per kilogram of body weight per week were predicted to result in trough plasma concentrations of emicizumab of 45 μg per milliliter (dashed line). I bars indicate standard deviations.

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alone. Thrombotic microangiopathy or thrombosis occurred only in patients who received high cumulative doses of activated prothrombin complex concentrate for breakthrough bleeding while receiving emicizumab prophylaxis; thus, the usefulness of this bypassing agent may be limited in patients who have bleeding events while receiving emicizumab prophylaxis. Emicizumab may provide a weekly, subcutaneous, prophylactic therapeutic option for patients with hemophilia A with inhibitors.

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