ORIGINAL ARTICLE

Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B

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ABSTRACT

BACKGROUND

Prophylactic factor replacement in patients with hemophilia B improves outcomes but requires frequent injections. A recombinant factor IX Fc fusion protein (rFIXFc) with a prolonged half-life was developed to reduce the frequency of injections required.

METHODS

We conducted a phase 3, nonrandomized, open-label study of the safety, efficacy, and pharmacokinetics of rFIXFc for prophylaxis, treatment of bleeding, and perioperative hemostasis in 123 previously treated male patients. All participants were 12 years of age or older and had severe hemophilia B (endogenous factor IX level of ≤2 IU per deciliter, or ≤2% of normal levels). The study included four treatment groups: group 1 received weekly dose-adjusted prophylaxis (50 IU of rFIXFc per kilogram of body weight to start), group 2 received interval-adjusted prophylaxis (100 IU per kilogram every 10 days to start), group 3 received treatment as needed for bleeding episodes (20 to 100 IU per kilogram), and group 4 received treatment in the perioperative period. A subgroup of group 1 underwent comparative sequential pharmacokinetic assessments of recombinant factor IX and rFIXFc. The primary efficacy end point was the annualized bleeding rate, and safety end points included the development of inhibitors and adverse events.

RESULTS

As compared with recombinant factor IX, rFIXFc exhibited a prolonged terminal half-life (82.1 hours) ($P<0.001$). The median annualized bleeding rates in groups 1, 2, and 3 were 3.0, 1.4, and 17.7, respectively. In group 2, 53.8% of participants had dosing intervals of 14 days or more during the last 3 months of the study. In groups 1, 2 and 3, 90.4% of bleeding episodes resolved after one injection. Hemostasis was rated as excellent or good during all major surgeries. No inhibitors were detected in any participants receiving rFIXFc; in groups 1, 2, and 3, 73.9% of participants had at least one adverse event, and serious adverse events occurred in 10.9% of participants. These events were mostly consistent with those expected in the general population of patients with hemophilia.

CONCLUSIONS

Prophylactic rFIXFc, administered every 1 to 2 weeks, resulted in low annualized bleeding rates in patients with hemophilia B. (Funded by Biogen Idec; ClinicalTrials.gov number, NCT01027364.)

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In patients with severe hemophilia B, recurrent bleeding leads to painful hemarthroses, disabling hemophilic arthropathy, and other sequelae.[1,2] Prophylactic replacement of coagulation factor IX is associated with improved clinical outcomes[3-7]; however, the relatively short half-lives of currently available factor IX products necessitate frequent intravenous injections (two or three times weekly) to maintain protective levels (at or above 1 IU per deciliter).[8,9] The frequency of injections is a considerable burden, cited by patients as a key deterrent to undertaking prophylactic treatment.[10] Various strategies to reduce this burden and improve the treatment of hemophilia B are under investigation,[11,12] including the use of bioengineered coagulation factors, which may require less frequent injections,[13-17] and gene-transfer therapy,[18,19] a potentially curative treatment option.

To prolong the half-life and reduce the frequency of injections, recombinant factor IX Fc fusion protein (rFIXFc), or eftrenonacog alfa, has been developed. The protein is composed of a single molecule of recombinant factor IX covalently fused to the dimeric Fc domain of IgG_1.[15,17] With Fc fusion proteins, the neonatal Fc receptor and the endogenous IgG recycling pathway delay lysosomal degradation of IgG and the fusion proteins, recycling them back into circulation and thus prolonging the plasma half-life.[20,21] The pharmacokinetics and safety of rFIXFc were previously evaluated in a single-dose, phase 1–2a clinical study involving patients with severe hemophilia B.[17] Here we report the results of a phase 3 nonrandomized, open-label, multicenter study designed to compare the pharmacokinetics of rFIXFc with those of recombinant factor IX and to assess the safety and efficacy of repeated administration of rFIXFc for the prevention and treatment of bleeding in adolescents and adults with severe hemophilia B.

Methods

Study Oversight

The protocol (available with the full text of this article at NEJM.org) was developed by the sponsor of the study, Biogen Idec, in collaboration with the Food and Drug Administration for a prelicensure study and was approved by the institutional review board at each participating center. The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice. Data were collected by the investigators and analyzed by the sponsor. All authors had access to the final data, participated in data analysis and interpretation, and vouch for the completeness and accuracy of the data and adherence to the study protocol. The first draft of the manuscript was written by three of the authors (two were employees of the sponsor, and the third a paid consultant to the sponsor) with input from all coauthors and with assistance from a medical writer funded by the sponsor. All authors participated in revising subsequent drafts of the manuscript and made the final decision to submit it for publication. Biogen Idec reviewed the manuscript and provided feedback to the authors.

Study Participants

Male patients 12 years of age or older with severe hemophilia B (≤2 IU of endogenous factor IX per deciliter) were eligible for inclusion in the study if they were receiving prophylaxis or had a history of at least eight bleeding events in the year before enrollment and had been previously treated with at least 100 injections of replacement factor IX (i.e., had accrued at least 100 exposure days). Patients were excluded if they had a history of development of inhibitors (i.e., neutralizing antibodies) or anaphylaxis associated with factor IX or intravenous immunoglobulin. Patients with other coagulation disorders, uncontrolled infection with the human immunodeficiency virus (HIV), renal dysfunction, or active hepatic disease were also excluded from the study. All patients or their guardians provided written informed consent.

Study Design

Participants were assigned to one of four treatment groups (Fig. 1) by an investigator on the basis of the clinical site's standard of care. Group 1 received weekly prophylaxis with 50 IU of rFIXFc per kilogram of body weight to start, with the dose adjusted as needed; group 2 received interval-adjusted prophylaxis with 100 IU of rFIXFc per kilogram at intervals of 10 days to start, with the interval adjusted as needed; group 3 received episodic (on-demand) treatment consisting of 20 to 100 IU of rFIXFc per kilogram for bleeding episodes, with the dose adjusted according to bleeding severity; and group 4 received treatment with rFIXFc as part of perioperative care. The dose (in group 1) and the interval (in group 2) were adjusted during the study to maintain a trough level of 1 to 3 IU per deciliter above baseline, or higher

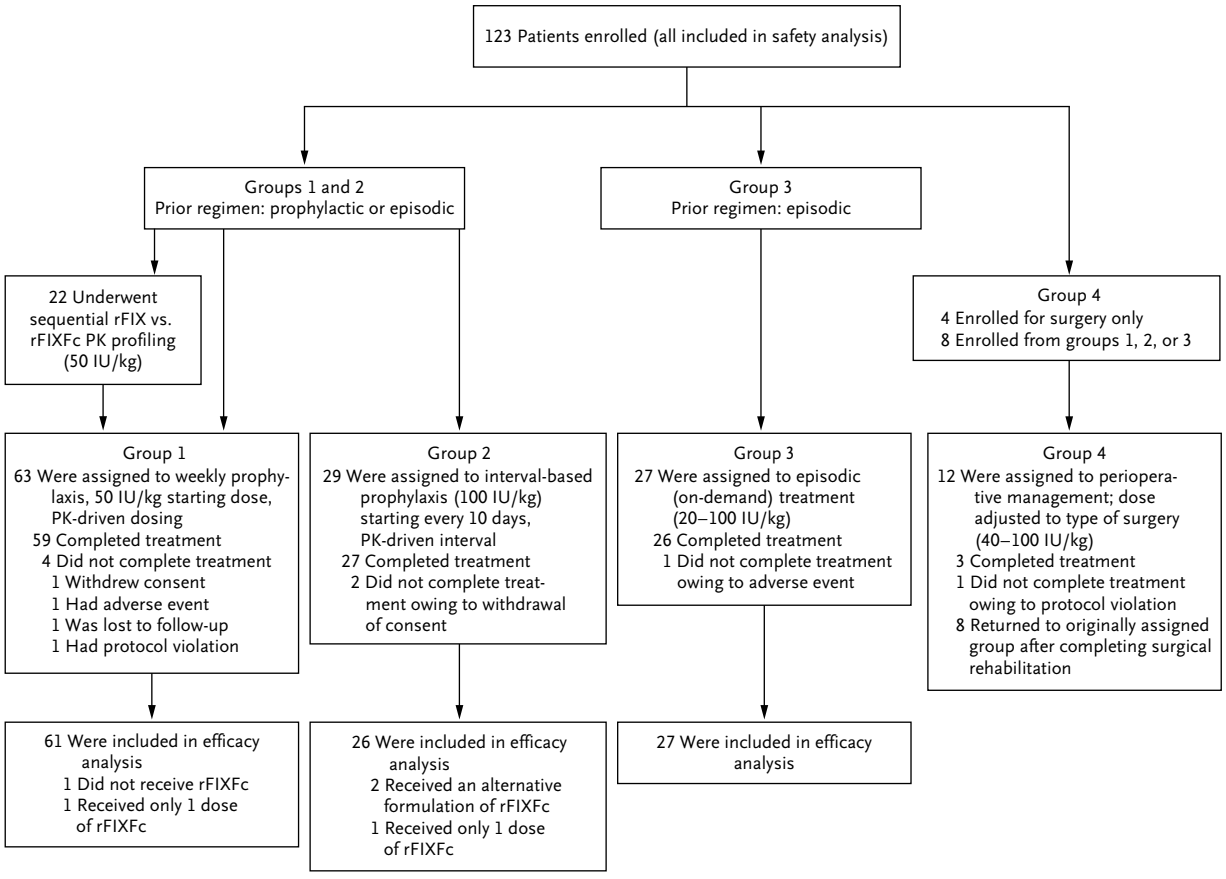

Figure 1. Numbers of Patients Who Were Enrolled, Assigned to a Study Group, and Included in the Efficacy Analysis.

After screening, patients who had been receiving a prophylactic regimen could enroll in group 1 or 2, whereas those who had been receiving episodic treatment could enroll in any treatment group. The regimen history was unknown for 1 participant in group 1. Participants meeting the criteria for study inclusion who required major surgery could enter group 4 either directly or from group 1, 2, or 3. Complete pharmacokinetic (PK) profiles for recombinant factor IX (rFIX) and recombinant factor IX Fc fusion protein (rFIXFc) were available for 22 participants at baseline. Two participants were withdrawn from the study because of adverse events (an infection and a motorcycle accident); both participants were hospitalized in countries where the study drug could not be imported; therefore, the study treatment was discontinued and the patients were withdrawn from the study. Owing to a change in the manufacturing process for rFIXFc, participants who had received only an earlier form of rFIXFc were excluded from the efficacy analysis.

if clinically necessary. The study was terminated when 53 participants had 50 or more rFIXFc exposure days (i.e., administration of one or more rFIXFc injections in a 24-hour period) in conjunction with additional criteria (specified in the Supplementary Appendix, available at NEJM.org).

In a subgroup of participants in group 1, we performed sequential pharmacokinetic assessments of an approved recombinant factor IX product (BeneFIX, Pfizer) and rFIXFc. At baseline, a dose of 50 IU of recombinant factor IX per kilogram was injected and the pharmacokinetics were assessed for 96 hours, followed by a washout period of 120 hours and subsequent injection of 50 IU of rFIXFc per kilogram, with the pharmacokinetics assessed for 240 hours. Pharmacokinetic assessment in this subgroup was repeated at week 26, with results that were consistent with the baseline findings.

OUTCOME MEASURES

The primary efficacy end point was the per-patient annualized bleeding rate (the number of bleeding episodes per participant divided by the number of days in the efficacy period, multiplied by 365.25). Primary safety end points were the development of inhibitors (detected with the use of a Nijmegen-modified Bethesda assay and confirmed on repeat

testing within 2 to 4 weeks if the titer reached 0.6 Bethesda units or more per milliliter) and adverse events. Secondary end points included pharmacokinetic measures, the weekly dose of rFIXFc (in group 1), the dosing interval (in group 2), and the number of injections and dose per injection required to resolve a bleeding episode. Additional safety evaluations included assessment of non-neutralizing antibodies by means of an electrochemiluminescence assay for rFIXFc-binding antibodies,[22,23] and measurements of laboratory markers (see the Supplementary Appendix). The rating of hemostasis provided by the site investigator or surgeon during the perioperative period was also evaluated.

STATISTICAL ANALYSIS

Efficacy analyses were performed with the use of data from participants who received one or more doses of rFIXFc during the efficacy period, not including the perioperative or surgical rehabilitation period (i.e., the time from hospital discharge to 1 minute before the first prophylactic dose for groups 1 and 2 or, for group 3, the date of completion of the rehabilitation period). Safety analyses included data from participants who received one or more doses of rFIXFc or recombinant factor IX. Comparisons of prophylaxis with episodic treatment (groups 1 and 2 vs. group 3) were based on annualized estimates of bleeding rates calculated with the use of a negative binomial regression model. Descriptive statistics included medians and interquartile ranges for groups 1, 2, and 3. Pharmacokinetic measures of rFIXFc and recombinant factor IX were compared with the use of a repeated-measures analysis-of-variance model with variables for study treatment and participant; 95% confidence intervals were calculated for geometric means and for the intraparticipant ratio of rFIXFc to recombinant factor IX for each pharmacokinetic measure. For all tests, a two-sided alpha level of 5% was considered to indicate statistical significance. The incidence of inhibitor development was assessed with the use of a group sequential design, with interim analyses conducted after at least 53 participants with 50 or more exposure days to rFIXFc had undergone testing for the detection of inhibitors (see the Supplementary Appendix). The study was sufficiently powered to detect, with 95% confidence, a clinically meaningful difference of 50% or more reduction in the annualized bleeding rate (group 1 vs. group 3) and to rule out an estimated incidence of inhibitor development of more than 10.65%.[24]

RESULTS

STUDY POPULATION

A total of 123 male patients were enrolled at 50 investigational sites in 17 countries between January 22, 2010, and July 19, 2012. A total of 115 participants (93.5%) completed the study (Fig. 1). Baseline characteristics (Table 1) showed a demographically diverse population, including many patients with HIV or hepatitis C virus infection. The genotype profile was consistent with expectations in this population (with a missense mutation detected in 55% of participants). Enrollment of the prophylaxis cohorts (groups 1 and 2) maintained a balanced distribution of prior regimens and previous bleeding episodes. More than 80% of participants who reported previous use of prophylaxis were receiving injections two or more times weekly. In groups 1, 2, and 3, the median durations of treatment were 51.6 weeks (range, <1 to 97), 58.3 weeks (range, <1 to 126), and 40.9 weeks (range, 28 to 54), respectively, and the median numbers of exposure days were 55.0 (range, 1 to 105), 38.0 (range, 1 to 71), and 16.0 (range, 4 to 35), respectively. A total of 5243 rFIXFc injections were administered during the study, corresponding to 5144 exposure days (117.1 patient-years of exposure). Overall, 96.6% of participants in the prophylaxis groups were adherent to their treatment regimen (i.e., took ≥80% of doses at the prescribed dose and ≥80% of doses at the prescribed interval) (95.1% in group 1 and 100% in group 2). Most participants self-administered rFIXFc at home.

PHARMACOKINETIC MEASURES

In the pharmacokinetics subgroup, 22 participants completed the baseline pharmacokinetic assessments for both recombinant factor IX and rFIXFc. The terminal half-life of rFIXFc was significantly longer than that of recombinant factor IX (geometric mean, 82.1 vs. 33.8 hours; P<0.001) (Fig. 2, and Tables S1 and S2 in the Supplementary Appendix). The incremental recovery levels for rFIXFc and recombinant factor IX were similar (0.92 and 0.95 IU per deciliter per international unit per kilogram, respectively). The time to reach a factor IX level of 1 IU per deciliter (1%) was 11.2 days with rFIXFc and 5.1 days with recombinant factor IX (Fig. 2, and Table S1 in the Supplementary Appendix). The pharmacokinetic findings at week 26 were consistent with those at baseline (data not shown).

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Group 1: Weekly Prophylaxis (N=63)	Group 2: Interval-Adjusted Prophylaxis (N=29)	Group 3: Episodic Treatment (N=27)	Total (N=119)†
Age — yr				
Median	28	33	36	30
Range	12–71	12–62	14–64	12–71
Weight — kg				
Median	70.2	76.0	65.0	72.0
Range	45.2–186.7	50.0–128.0	45.0–91.7	45.0–186.7
Race or ethnic group — no. (%)				
White	41 (65.1)	18 (62.1)	11 (40.7)	70 (58.8)
Black	7 (11.1)	2 (6.9)	1 (3.7)	10 (8.4)
Asian	7 (11.1)	7 (24.1)	14 (51.9)	28 (23.5)
Other‡	8 (12.7)	2 (6.9)	1 (3.7)	11 (9.2)
Geographic location — no. (%)				
Europe	21 (33.3)	12 (41.4)	2 (7.4)	35 (29.4)
North America	18 (28.6)	7 (24.1)	11 (40.7)	36 (30.3)
Other§	24 (38.1)	10 (34.5)	14 (51.9)	48 (40.3)
Factor IX level — no. (%)				
<1 IU/dl	50 (79.4)	22 (75.9)	26 (96.3)	98 (82.4)
1–2 IU/dl	13 (20.6)	7 (24.1)	1 (3.7)	21 (17.6)
Prestudy factor IX therapy — no. (%)¶				
Prophylaxis	33 (53.2)	15 (51.7)	0	48 (40.7)
Episodic treatment	29 (46.8)	14 (48.3)	27 (100.0)	70 (59.3)
Estimated no. of bleeding episodes in prior 12 mo				
Overall				
Median	10.5	10.0	18.0	12.0
Range	0–70	0–100	5–50	0–100
With prior prophylaxis				
Median	2.5	2.0	NA	2.0
Range	0–21	0–7	NA	0–21
With prior episodic treatment	23.0 (6–70)	25.0 (10–100)	18.0 (5–50)	22.0 (5–100)
≥1 Target joint — no. (%)	36 (57.1)	8 (27.6)	14 (51.9)	58 (48.7)
HIV-positive — no. (%)	5 (7.9)	1 (3.4)	2 (7.4)	8 (6.7)
HCV-positive — no. (%)	38 (60.3)	15 (51.7)	14 (51.9)	67 (56.3)

* HCV denotes hepatitis C virus, HIV human immunodeficiency virus, and NA not applicable.
† The four participants who were enrolled only in the perioperative surgery group are not included.
‡ Other races and ethnic groups include Native American or Alaska Native, Hispanic, and mixed races (e.g., white and Asian or white and black).
§ Other locations included Australia, Brazil, China, India, Japan, and South Africa.
¶ The prestudy regimen was unknown for one participant in group 1; percentages were calculated on the basis of participants for whom data were complete.

EFFICACY

Prophylactic treatment significantly reduced the annualized rate of bleeding in group 1 (by 83%) and group 2 (by 87%) as compared with the rate in the group receiving episodic treatment, according to estimates from a negative binominal regression model (3.12, 2.40, and 18.67 for groups 1, 2, and 3, respectively; P<0.001) (Table 2). The median weekly rFIXFc dose with weekly prophylaxis (group 1) was 45 IU per kilogram (starting dose, 50 IU per kilogram), and the median dosing interval with interval-adjusted prophylaxis

(group 2) was 12.5 days (starting interval, 10 days) (Table 2, and Fig. S1 in the Supplementary Appendix). Among the participants in group 2 who were in the study for 6 or more months, 14 participants (53.8%) had a dosing interval that was 14 or more days during the last 3 months of the study.

The reduction in the annualized bleeding rate with prophylaxis as compared with episodic treatment was consistent across all demographic and disease-based subgroups in prespecified subgroup analyses (Fig. 3 and Table 2). Participants who received prophylaxis and had previously received episodic treatment had lower median annualized bleeding rates during the study than during the 12-month period before study entry (group 1, 2.5 vs. 23.0; group 2, 1.9 vs. 25.0); this reduction in bleeding rates was not observed in participants who continued to receive episodic treatment (group 3, 17.7 vs. 18.0). Participants in groups 1, 2, and 3 with the highest bleeding frequency before study entry (≥36 bleeding episodes) had median annualized bleeding rates of 2.05, 2.76, and 29.43, respectively, while enrolled in the study. Among the participants receiving prophylaxis, 23.0% in group 1 and 42.3% in group 2 had no bleeding episodes during the study.

A total of 636 bleeding episodes, primarily spontaneous joint bleeding, occurred during the efficacy period. One injection was sufficient to resolve 90.4% of bleeding episodes; 97.3% were resolved with one or two injections. The median dose per injection required to resolve bleeding episodes was 46 IU per kilogram (Table S3 in the Supplementary Appendix). For bleeding episodes that required more than one injection for resolution, the median interval between the first and second injection was 45 hours. In 14 major surgeries performed in 12 participants, including 5 knee replacements, the hemostatic response during the perioperative period was rated by investigators or surgeons as excellent (for 13 surgeries) or good (for 1).

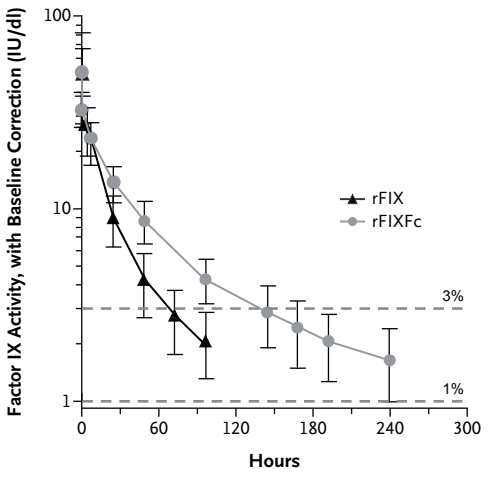

Figure 2. Duration of Factor IX Activity with Recombinant Factor IX and rFIXFc at a Dose of 50 IU per Kilogram of Body Weight.

The data presented represent factor IX activity (mean ±SD) for each treatment group. The dashed lines indicate factor IX trough levels of 1 IU per deciliter (1%) and 3 IU per deciliter (3%). Pharmacokinetic measures were assessed for 22 participants at baseline. The terminal half-life of rFIXFc (geometric mean, 82.1 hours) was significantly longer than that of rFIX (geometric mean, 33.8 hours, based on a 96-hour sampling schedule) ($P<0.001$). The half-life of rFIX, calculated on the basis of the traditional 48-hour pharmacokinetic sampling schedule, was 17.04 hours (95% confidence interval [CI], 15.89 to 18.26), which is similar to previously reported 48-hour data.[25] Clearance was significantly lower for rFIXFc (3.2 ml per hour per kilogram of body weight; 95% CI, 2.8 to 3.6) than for rFIX (6.3 ml per hour per kilogram; 95% CI, 5.6 to 7.1). The dose-normalized area under the curve was 31.3 IU × hour per deciliter per international unit per kilogram (95% CI, 27.9 to 35.2) and 15.8 IU × hour per deciliter per IU per kilogram (95% CI, 14.0 to 17.7) for rFIXFc and rFIX, respectively. Times to 1 and 3 IU per deciliter above baseline were 11.2 days (95% CI, 10.2 to 12.4) and 5.8 days (95% CI, 5.1 to 6.6), respectively, for rFIXFc versus 5.1 days (95% CI, 4.6 to 5.7) and 2.8 days (95% CI, 2.6 to 3.1), respectively, for rFIX ($P<0.001$).

SAFETY

Inhibitors were not detected in any participants with test results that could be evaluated, including 55 participants with 50 or more exposure days, for whom the inhibitor incidence was 0% (95% confidence interval [CI], 0 to 6.5); the inhibitor incidence overall was also 0% (95% CI, 0 to 3.0). In the safety-analysis population, non-neutralizing antibodies were detected at a low titer or at a borderline-positive titer (defined as a maximum level two times as high as the lowest measurable titer) in three participants before exposure to rFIXFc; all three had negative test results during the study. One participant who had a borderline-negative test result (two of three screening-assay results just below the limit of detection) before exposure to rFIXFc had a borderline-positive result at the end of study. These transient and low antibody titers did not affect the pharmacokinetics of rFIXFc and had no discernible clinical effect.

Among the 119 participants in groups 1, 2, and 3, a total of 88 (73.9%) had at least one ad-

verse event during the rFIXFc treatment period (excluding adverse events that occurred during the perioperative period) (Table S4 in the Supplementary Appendix). The most common adverse events (with an incidence ≥5% in a pooled analysis of groups 1, 2, and 3) were nasopharyngitis, influenza, arthralgia, upper respiratory tract infection, headache, and hypertension. The majority of these events were judged by the investigators to be unrelated or unlikely to be related to treatment with rFIXFc. Thirteen of the 119 participants (10.9%) had at least one serious adverse event. One participant had a single serious adverse event that was considered to be possibly related to treatment with rFIXFc. In this participant, who had a history of painful hematuria, an obstructive clot developed in the urinary collecting system. The clot resolved with medical management, and the participant continued with the study treatment and completed the study. There were no reports of vascular thrombotic events, serious hypersensitivity, or anaphylaxis, and there were no deaths during the study. No unique safety concerns were identified in participants undergoing major surgery.

DISCUSSION

This phase 3 study confirmed data from a phase 1–2a study showing the prolonged half-life of rFIXFc, as compared with recombinant factor IX,[17] and showed that rFIXFc had an acceptable safety profile and was effective in the prevention and treatment of bleeding in previously treated adolescents and adults with severe hemophilia B. All participants who received prophylactic rFIXFc, including those with a high frequency of bleeding before study entry, had marked reductions in the annualized bleeding rate, as compared with patients who received episodic treatment. Before study entry, 80% or more of participants treated prophylactically required injections at least two times per week, whereas during the study, prophylaxis was effective with injections administered every 1 to 2 weeks. These dosing intervals are longer than those observed in previous trials of recombinant factor IX.[25-27]

The neonatal Fc-receptor–mediated extension of half-life was apparent in the intraparticipant comparison of the pharmacokinetics of rFIXFc and recombinant factor IX. The terminal half-life of rFIXFc was 82.1 hours. The terminal half-life for recombinant factor IX (33.8 hours), which we calculated by means of pharmacokinetic sampling over the course of 96 hours, was substantially longer than that reported in some previous studies on the basis of 48-hour sampling (terminal half-life, approximately 18 hours),[14,16,25,26,28] whereas it was more in line with the terminal half-life in studies that performed 72-hour sampling (terminal half-life, 21.3 to 33.4 hours).[13,27,29-31] When we analyzed the pharmacokinetics of recombinant factor IX on the basis of sampling for only 48 hours (Table S2 in the Supplementary Appendix), the terminal half-life was 17.0 hours, which is consistent with the results of the studies using 48-hour sampling, thus confirming the method used in our analysis of recombinant factor IX. All clearance-dependent pharmacokinetic measures in this study were prolonged with rFIXFc as compared with recombinant factor IX and remained stable over the course of long-term treatment, suggesting that the pharmacokinetics of rFIXFc may be used to individualize dosing regimens.

Adverse events observed in this study were consistent with those expected in the population of persons with hemophilia,[27] and the rate of study completion was high (93.5%). Inhibitors of rFIXFc were not detected in any participant, including 55 participants who were followed for 50 or more exposure days. Inhibitors generally develop within the first 50 exposure days of factor IX replacement therapy[32]; they can pose a challenge to the establishment of hemostasis and can be associated with anaphylaxis.[33,34] Since participants with a history of inhibitors to factor IX were excluded from the study, which was limited to previously treated patients (a patient population at low risk for the development of inhibitors),[35,36] further clinical study is needed to assess the likelihood of the development of inhibitors of rFIXFc in previously untreated patients and to determine whether patients with a history of the development of inhibitors to factor IX will benefit from rFIXFc.

Although the incidence of non-neutralizing antibodies in patients with hemophilia B is unknown, such antibodies have been reported in up to 30% of patients with hemophilia A.[37,38] In this study, non-neutralizing antibodies were observed at low titers in 3% of participants before treatment with rFIXFc began, but their presence was transient and had no discernible effect on the pharmacokinetics of rFIXFc or on bleeding rates. The clinical significance of non-neutralizing antibodies is not well understood and requires further longitudinal study.

Clinical trial design for patients with hemophilia B presents a challenge to investigators owing to the small population of patients and ethical considerations that preclude the conduct of placebo-controlled studies in which participants are unaware of the group assignment.[39,40] Although our study included a controlled intraparticipant comparison of the pharmacokinetics of rFIXFc and recombinant factor IX, it did not include an active-comparator control group for the evaluation of trial end points. The study was designed to allow a participant's treatment regimen to be consistent with current clinical practice. It would have been unethical to allow a participant who had been receiving a prophylactic regimen to undergo randomization to an episodic regimen, given that prophylaxis is the standard of care in many regions of the world. Thus, treatment assignments were performed in a nonrandomized manner, with every effort made to balance the prophylactic treatment groups with respect to prior regimens and the history of bleeding.

Since determination of the efficacy of prophylaxis was based on nonrandomized comparisons with episodic treatment, there is potential for bias. However, multiple subgroup analyses supported the primary efficacy results, including an analysis limiting the comparison to participants who had received episodic treatment before study entry, which revealed a reduction in the annualized bleeding rate during prophylactic therapy that was similar to that observed in the primary analysis. There is evidence that participants with prior episodic treatment and a high frequency of bleeding episodes may have preferentially elected to enter the prophylaxis groups (i.e., bleeding rates in the 12 months preceding study entry were higher among participants in groups 1 and 2 who had been receiving episodic treatment than among participants in group 3). Allowing participants to elect to enter a prophylactic group may introduce self-selection bias. The potential for confounding remains; however, it is unlikely that the magnitude of the reduction in bleeding rates with prophylaxis as compared with episodic treatment is the result of confounding alone.

Table 2. Efficacy End Points for Weekly Prophylaxis, Interval-Adjusted Prophylaxis, and Episodic Treatment.

End Point	Group 1: Weekly Prophylaxis (N=61)	Group 2: Interval-Adjusted Prophylaxis (N=26)	Group 3: Episodic Treatment (N=27)
Annualized bleeding rate (95% CI)*	3.12 (2.46–3.95)	2.40 (1.67–3.47)	18.67 (14.01–24.89)
Reduction in annualized bleeding rate vs. group 3 — %*	83 (<0.001)	87 (<0.001)	
Annualized bleeding rate			
Overall	3.0 (1.0–4.4)	1.4 (0.0–3.4)	17.7 (10.8–23.2)
Spontaneous	1.0 (0.0–2.2)	0.9 (0.0–2.3)	11.8 (2.6–19.8)
Traumatic	1.0 (0.0–2.1)	0.0 (0.0–0.8)	2.2 (0.0–6.8)
Joint	1.1 (0.0–4.0)	0.4 (0.0–3.2)	13.6 (6.1–21.6)
Spontaneous	1.0 (0.0–2.1)	0.0 (0.0–1.7)	5.1 (2.6–17.3)
Traumatic	0.0 (0.0–1.1)	0	1.3 (0.0–3.6)
Muscle	0.0 (0.0–1.0)	0	4.0 (1.0–6.8)
Spontaneous	0	0	1.0 (0.0–3.6)
Traumatic	0	0	1.1 (0.0–2.7)
Baseline trough level of factor IX†			
<1 IU/dl			
Median	2.6	1.1	18.5
Interquartile range	1.0–4.1	0.0–2.9	13.2–23.2
1–2 IU/dl			
Median	4.5	3.4	7.7
Interquartile range	0.0–6.4	0.0–5.7	7.7–7.7

Table 2. (Continued.)

End Point	Group 1: Weekly Prophylaxis (N=61)	Group 2: Interval-Adjusted Prophylaxis (N=26)	Group 3: Episodic Treatment (N=27)
Dose for weekly prophylaxis — IU/kg‡			
Overall			
Median	45.2		
Range	25.0–74.3		
Last 6 mo in study			
Median	40.7		
Range	21.3–82.7		
Last 3 mo in study			
Median	40.5		
Range	16.7–87.6		
Interval for interval-adjusted prophylaxis — no. of days‡			
Overall			
Median		12.5	
Range		7.8–15.9	
Last 6 mo in study			
Median		13.8	
Range		7.8–19.1	
Last 3 mo in study			
Median		14.0	
Range		7.7–20.8	

* Annualized bleeding rates (the number of bleeding episodes per participant divided by the number of days in the efficacy period, multiplied by 365.25) were calculated with the use of the negative binomial regression model to control for participants' time in the study. CI denotes confidence interval. P<0.001 for the rate reductions in groups 1 and 2 as compared with group 3.

† The baseline trough level was the minimum factor IX level measured in screening and baseline laboratory tests. In groups 1, 2, and 3, the numbers of participants with trough levels of less than 1 IU per deciliter were 48, 21, and 26, respectively, and the numbers with levels between 1 and 2 IU per deciliter were 13, 5, and 1, respectively.

‡ Changes in pharmacokinetically driven dosing for groups 1 and 2 were allowed to achieve trough levels that were 1 to 3 IU per deciliter above baseline. If participants had two breakthrough spontaneous bleeding episodes in a rolling 3-month period, the dose (in group 1) or the interval (in group 2) could be adjusted to provide more protection. The numbers of participants who remained in the study for 9 or more months were 58 in group 1 and 26 in group 2; the numbers were the same for participants who remained in the study for 6 or more months.

This study was not designed to compare the two prophylactic regimens. Both the weekly dosing and interval-adjusted dosing regimens resulted in significantly reduced annualized rates of bleeding, as compared with episodic treatment. Whether one approach to dosing is superior to the other cannot be determined on the basis of this study. In clinical practice, the two approaches may offer patients the choice between more frequent dosing (e.g., weekly dosing), which would maintain higher trough levels of factor IX, providing greater protection, and less frequent dosing, which would result in lower trough levels but would reduce the required frequency of injections.

In conclusion, this study showed that rFIXFc is safe and effective for the treatment and prevention of bleeding events, including those incurred during major surgeries, in previously treated adolescents and adults with hemophilia B. Fc fusion did not impair factor IX activity or result in increased immunogenicity. The prolonged half-life of rFIXFc allowed for effective prophylaxis, with injections every 1 to 2 weeks.

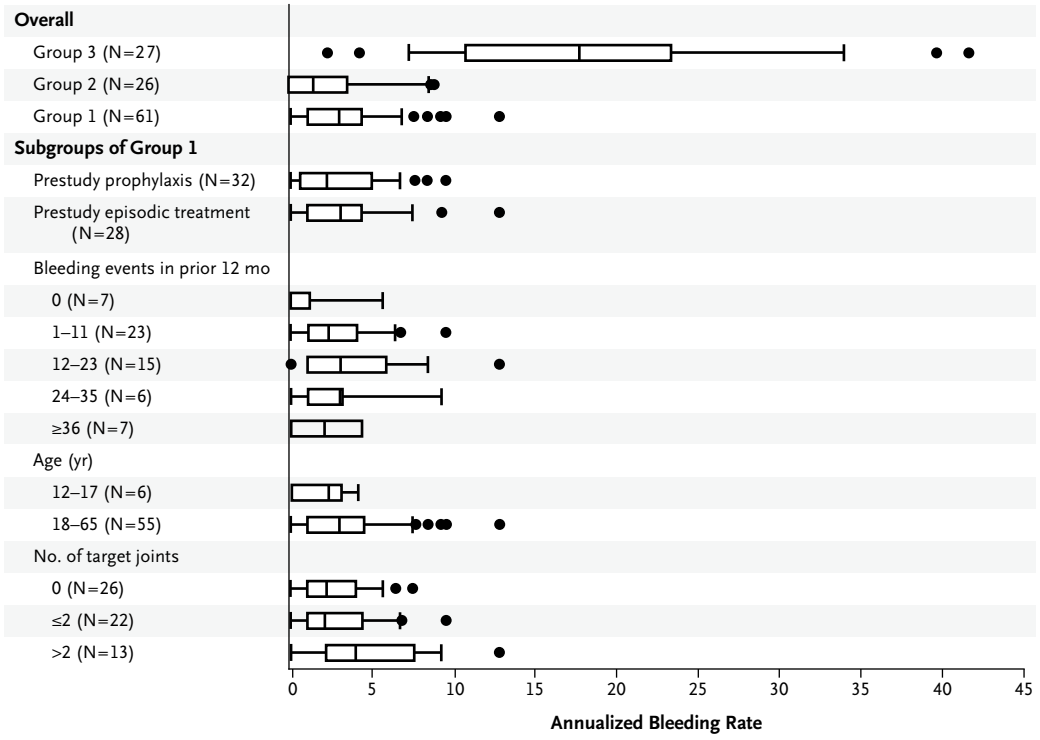

Figure 3. Annualized Bleeding Rate in Groups 1, 2, and 3 and Subgroups of Group 1.

The results of all subgroup analyses were consistent with the results of the primary efficacy analysis, with a reduction in bleeding rates in groups 1 and 2 and all prespecified subgroups of group 1. Group 1 was the only group in which there was a sufficient number of participants to display subgroup analyses graphically. The bars within the boxes indicate the medians; the ends of the boxes represent the interquartile range from 25 to 75%, and the bars outside the boxes represent the range from 10 to 90%; circles represent outliers (individual participants). The prestudy treatment regimen was unknown for one participant in group 1.

The potential for higher trough levels of rFIXFc or longer intervals between doses may lead to greater use of prophylaxis among patients with hemophilia B.

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APPENDIX

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