ORIGINAL ARTICLE

BIVV001 Fusion Protein as Factor VIII Replacement Therapy for Hemophilia A

Barbara A. Konkle, M.D., Amy D. Shapiro, M.D., Doris V. Quon, M.D., Ph.D., Janice M. Staber, M.D., Roshni Kulkarni, M.D., Margaret V. Ragni, M.D., M.P.H., Ekta S. Chhabra, Ph.D., Stacey Poloskey, M.D., Kara Rice, M.S., Suresh Katragadda, Ph.D., Joachim Fruebis, Ph.D., and Craig C. Benson, M.D.

ABSTRACT

BACKGROUND

Factor VIII replacement products have improved the care of patients with hemophilia A, but the short half-life of these products affects the patients' quality of life. The half-life of recombinant factor VIII ranges from 15 to 19 hours because of the von Willebrand factor chaperone effect. BIVV001 (rFVIIIFc-VWF-XTEN) is a novel fusion protein designed to overcome this half-life ceiling and maintain high sustained factor VIII activity levels. Data are lacking on the safety and pharmacokinetics of single-dose BIVV001.

METHODS

In this phase 1–2a open-label trial, we consecutively assigned 16 previously treated men (18 to 65 years of age) with severe hemophilia A (factor VIII activity, <1%) to receive a single intravenous injection of recombinant factor VIII at a dose of 25 IU per kilogram of body weight (lower-dose group) or 65 IU per kilogram (higher-dose group). This injection was followed by a washout period of at least 3 days. The patients then received a single intravenous injection of BIVV001 at the same corresponding dose of either 25 IU or 65 IU per kilogram. Adverse events and pharmacokinetic measurements were assessed.

RESULTS

No inhibitors to factor VIII were detected and no hypersensitivity or anaphylaxis events were reported up to 28 days after the injection of single-dose BIVV001. The geometric mean half-life of BIVV001 was three to four times as long as that of recombinant factor VIII (37.6 hours vs. 9.1 hours in the lower-dose group and 42.5 vs. 13.2 hours in the higher-dose group); the area under the curve (AUC) for product exposure was six to seven times as great in the two dose groups (4470 hours vs. 638 hours × IU per deciliter in the lower-dose group and 12,800 hours vs. 1960 hours × IU per deciliter in the higher-dose group). After the injection of BIVV001 in the higher-dose group, the mean factor VIII level was in the normal range (≥51%) for 4 days and 17% at day 7, which suggested the possibility of a weekly interval between treatments.

CONCLUSIONS

In a small, early-phase study involving men with severe hemophilia A, a single intravenous injection of BIVV001 resulted in high sustained factor VIII activity levels, with a half-life that was up to four times the half-life associated with recombinant factor VIII, an increase that could signal a new class of factor VIII replacement therapy with a weekly treatment interval. No safety concerns were reported during the 28-day period after administration. (Funded by Sanofi and Sobi; ClinicalTrials.gov number, NCT03205163.)

From Bloodworks Northwest and the University of Washington, Seattle (B.A.K.); Indiana Hemophilia and Thrombosis Center, Indianapolis (A.D.S.); the Orthopaedic Hemophilia Treatment Center, Los Angeles (D.V.Q.); the University of Iowa, Iowa City (J.M.S.); Michigan State University, East Lansing (R.K.); the Department of Medicine, University of Pittsburgh, and the Hemophilia Center of Western Pennsylvania, Pittsburgh (M.V.R.); and Sanofi (E.S.C., S.P., S.K., C.C.B.) and Bioverativ (K.R., J.F.) — both in Waltham, MA. Address reprint requests to Dr. Konkle at Bloodworks Northwest, 921 Terry Ave., Seattle, WA 98104, or at barbarak@bloodworksnw.org.

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Severe hemophilia A (defined as <1% endogenous factor VIII activity) can result in frequent spontaneous bleeding episodes and excessive bleeding after injury.[1] Without prophylactic replacement of factor VIII, patients may have more than 30 bleeding episodes per year,[1] some of which can be life-threatening (e.g., intracranial hemorrhage)[2] or cause major complications (e.g., recurrent bleeding in joints leading to hemarthropathy).[3] Therefore, a key goal and mainstay of treatment for patients with severe hemophilia is early and effective hemostasis with the use of prophylactic factor replacement to reduce mortality and preserve musculoskeletal function.[4]

Prophylaxis with factor VIII products that have an extended half-life has advanced the treatment of severe hemophilia, in part by improving the control of bleeding, joint health, and quality of life, and by reducing treatment burden.[5-8] However, residual burden still exists with current products[9,10] and may explain why treatment adherence in patients with severe hemophilia often remains less than ideal.[11]

Historically, the goal of prophylaxis for severe hemophilia A has been the maintenance of trough activity of plasma factor VIII of more than 1% (i.e., >1 IU per deciliter). This level was selected to achieve a factor VIII level that has been observed in patients with moderate hemophilia, regardless of the actual effect on outcomes. Associated with this goal has been a focus on the overall frequency of bleeding.[10,12-16] Treatment goals have expanded to include long-term outcomes associated with a higher sustained plasma factor VIII level, such as long-term joint protection and improved patient-reported quality of life and health equity.[14,16-21]

Factor VIII interacts in a noncovalent manner with endogenous von Willebrand factor (VWF), which stabilizes and protects factor VIII from proteases and clearance receptors.[22] VWF essentially acts as a chaperone, limiting the half-life of factor VIII therapy to approximately 15 hours.[23] Pegylation and Fc fusion techniques have moderately increased the factor VIII half-life by a factor of 1.5 to 2, as compared with factor VIII products with a standard half-life.[5,24-28] However, the VWF chaperone effect constrains the pharmacokinetics of such products with an extended half-life. Thus, the challenge of further increasing the half-life of factor VIII ultimately depends on the development of a new class of factor VIII replacement products that are decoupled from endogenous VWF.

BIVV001 (rFVIIIFc-VWF-XTEN) is a novel fusion protein that is designed to uncouple recombinant factor VIII from VWF in circulation. The product consists of a single recombinant factor VIII protein fused to dimeric Fc, a D′D3 domain of VWF (factor VIII–binding domain), and two XTEN polypeptides (Fig. 1A; and Figs. S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[29] Covalently linking a D′D3 domain of VWF to recombinant factor VIII prevents endogenous VWF binding, yet still maintains VWF-stabilizing characteristics. The half-life of recombinant factor VIII is further enhanced by fusion to the Fc domain of immunoglobulin G1 (IgG1),[30] as well as to two XTEN polypeptides.[31] XTENs are unstructured hydrophilic polypeptides that are designed to extend half-life through steric shielding.[32] Nonclinical studies have shown that the use of BIVV001 results in a half-life of factor VIII that is three to four times as long as that of recombinant factor VIII; such use also restores hemostasis in mice with factor VIII deficiency and does not interfere with in vitro human platelet function.[29,33] Here, we report the results of a single intravenous dose of BIVV001 with respect to safety and pharmacokinetics in patients with severe hemophilia A.

METHODS

POPULATION AND STUDY DESIGN

This phase 1–2a, open-label, dose-escalation study was conducted at six sites in the United States and one in Japan. At the time of screening, all the patients were required to be between 18 and 65 years of age, have severe hemophilia A, and have received previous therapy with a factor VIII product for at least 150 exposure days. Key exclusion criteria were measurable inhibitor activity on the Nijmegen-modified Bethesda assay, with a cutoff of at least 0.6 Bethesda units per milliliter for a positive result; a previous positive inhibitor test or a decreased clinical response to a factor VIII product; a plasma VWF ristocetin cofactor level of less than 50 IU per deciliter; a history of major surgery within 8 weeks before screening; and clinically significant disease that would confound participation in the study, such as a serious bacterial or viral infection within 30 days before screening or a coagu-

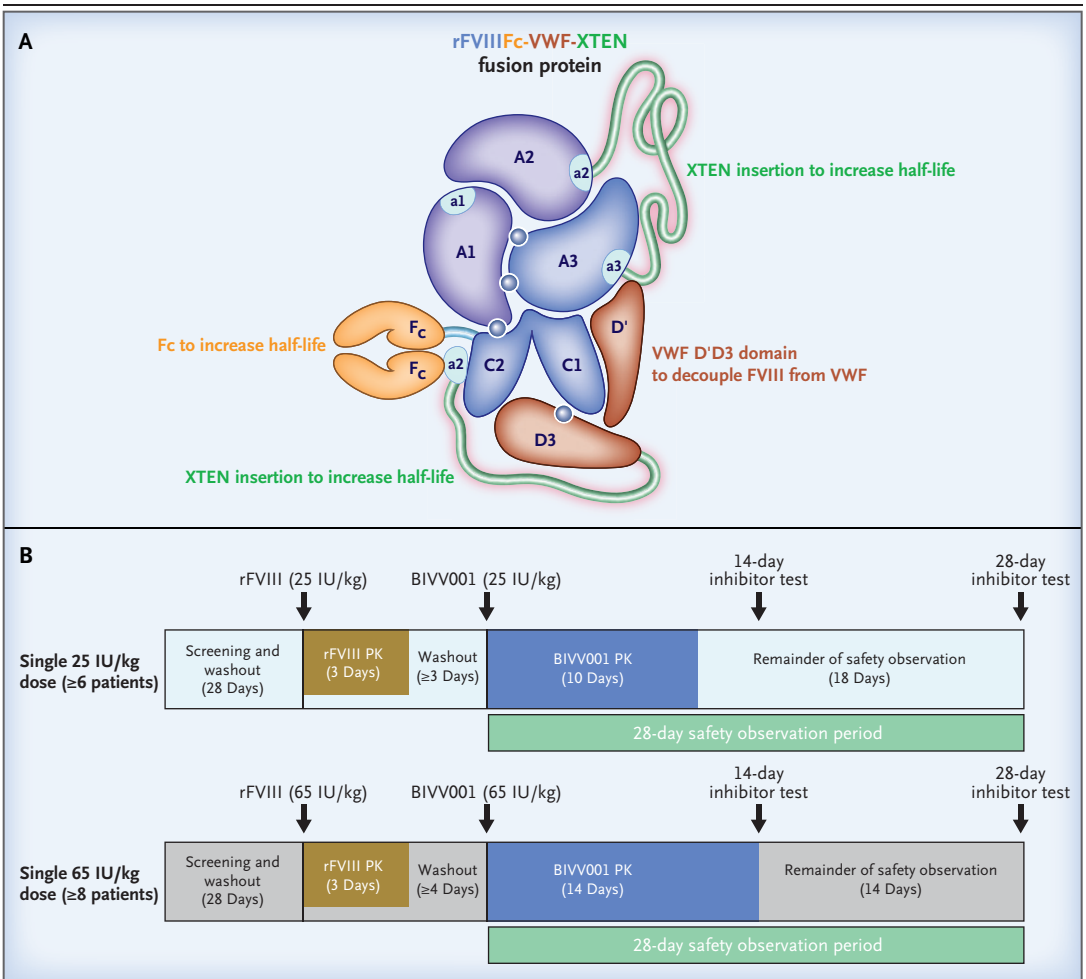

Figure 1. Structure of the BIVV001 Fusion Protein and Design of the Study.

Panel A shows the structure of BIVV001 (rFVIIIFc-VWF-XTEN), a novel fusion protein designed to uncouple recombinant factor VIII (rFVIII) from von Willebrand factor (VWF) in circulation. BIVV001 consists of a single rFVIII molecule fused to dimeric Fc, a D′D3 domain of VWF (factor VIII–binding domain), and two XTEN polypeptides to increase the half-life of factor VIII activity. Factor VIII (A1, A2, A3, C1, and C2) and VWF (D′D3) protein domains are annotated; a1, a2, and a3 (acidic regions [light blue circles]) represent natural factor VIII thrombin cleavage sites. Panel B shows the design of this open-label, dose-escalating study to evaluate the safety and pharmacokinetics (PK) of BIVV001, administered in a single dose by intravenous injection in patients with severe hemophilia A. Enrollment in the group that received 25 IU per kilogram of BIVV001 was completed first, followed by enrollment of a separate group of patients who received 65 IU per kilogram.

lation disorder in addition to hemophilia A. All the patients provided written informed consent before enrollment.

The primary objective was to assess the safety of a single intravenous dose of BIVV001. The secondary objective was to characterize and compare the pharmacokinetics of single-dose BIVV001 with that of full-length human recombinant factor VIII (Advate). The study consisted of the following three periods: an enrollment, screening, and prestudy period that included a washout period for previous factor VIII replacement for up to 28 days; a period for sampling the pharmacokinetic response to a single dose of recombinant factor VIII; and a period for the administration of BIVV001, sampling for pharmacokinetic response, and 28-day observation for safety (Fig. 1B).

STUDY TREATMENT

On day 1, the patients received an intravenous injection of recombinant factor VIII at a dose of either 25 IU per kilogram of body weight (lower-dose group) or 65 IU per kilogram (higher-dose group), which was followed by a washout period of at least 3 days. The patients then received an intravenous injection of BIVV001 at a corresponding dose of either 25 IU per kilogram or 65 IU per kilogram. Enrollment in the lower-dose cohort was completed first, followed by enrollment of a separate group of patients in the higher-dose cohort. The dose of 25 IU per kilogram was selected on the basis of the results of a nonclinical study of BIVV001 and an assessment of clinical and nonclinical results for marketed factor VIII products, including recombinant factor VIII Fc fusion protein. The dose of 65 IU per kilogram was determined by the upper limit of physiologic plasma factor VIII activity in healthy persons (150 IU per deciliter), as well as an anticipated incremental recovery of 2 IU per deciliter of factor VIII per IU per kilogram of BIVV001 on the basis of values that are typically observed.[34]

END POINTS

The primary end points were adverse events and clinically significant abnormalities on laboratory testing, including the development of inhibitors and changes in VWF activity (as measured on the VWF ristocetin cofactor assay) and in VWF antigen levels. The secondary end points were calculated pharmacokinetic measurements. (Details regarding the end points are provided in the Methods section in the Supplementary Appendix.)

PLASMA FACTOR VIII ACTIVITY, PHARMACOKINETICS, AND ANTIDRUG ANTIBODIES AND INHIBITORS

We measured plasma factor VIII activity using a one-stage activated partial thromboplastin time–based clotting assay (Dade Actin FSL Activated PTT Reagent, Siemens Healthcare) and a two-stage chromogenic assay (BIOPHEN FVIII:C, Hyphen BioMed); product-specific standard curves were generated for both assays. A blood sample was collected before the administration of factor VIII to confirm the presence of severe hemophilia A and to determine that washout had occurred before inhibitor testing. Subsequent blood samples were collected 3 and 4 days after the administration of recombinant factor VIII at doses of 25 IU and 65 IU per kilogram, respectively, and 10 and 14 days after the administration of the corresponding doses of BIVV001. Blood samples for inhibitor testing were collected on days 14 and 28 after the administration of BIVV001; inhibitor testing was performed with the use of the Nijmegen-modified Bethesda assay.

STUDY OVERSIGHT

The study was performed in accordance with the protocol (available at NEJM.org) and with the principles of the Declaration of Helsinki and local regulations. The study was initially sponsored by Bioverativ, which was acquired by Sanofi before the completion of the study, and by Sobi. All the authors had access to the primary clinical trial data and approved the decision to submit the manuscript for publication. Editorial support was provided by JK Associates and was funded by Sanofi.

STATISTICAL ANALYSIS

We used description statistics to summarize demographic and clinical characteristics according to the dose of BIVV001. No clinical efficacy assessments were performed. We used descriptive statistics to summarize adverse events in patients, both according to the dose level and overall, for the BIVV001 treatment period; adverse events were reported separately for the period in which patients received recombinant factor VIII. The mean plasma factor VIII activity over time was plotted for each dose level of recombinant factor FVIII and BIVV001. We summarized estimates for pharmacokinetic measurements according to the drug and dose level, and an analysis-of-variance model with factors for drug and patient was used to compare log-transformed pharmacokinetic measurements for the two products. Confidence intervals were not adjusted for multiple comparisons, and no formal interim analysis with hypothesis testing was completed. Periodic interim analyses were descriptive in nature.

RESULTS

PATIENTS

Of the 7 patients who were enrolled in the lower-dose group, all 7 received recombinant factor VIII and 6 received BIVV001 (Table 1). One patient was withdrawn from the study before receiving

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	25 IU/kg Group (N=7)	65 IU/kg Group (N=9)	All Patients (N=16)
Mean age (range) — yr	33 (19–60)	44 (32–63)	39 (19–63)
Mean weight (range) — kg	85.0 (67.2–100.6)	78.5 (59.9–100.7)	81.4 (59.9–100.7)
Race or ethnic group — no. (%)†			
White	6 (86)	7 (78)	13 (81)
Asian	1 (14)	1 (11)	2 (12)
Hispanic or Latino	1 (14)	0	1 (6)
Other	0	1 (11)	1 (6)
Geographic location — no. (%)			
United States	6 (86)	8 (89)	14 (88)
Japan	1 (14)	1 (11)	2 (12)
Class of condition in medical history — no. (%)‡			
Allergic	3 (43)	3 (33)	6 (38)
Cardiovascular	2 (29)	5 (56)	7 (44)
Genitourinary	1 (14)	5 (56)	6 (38)
Neurologic	1 (14)	4 (44)	5 (31)
Endocrine or metabolic	0	4 (44)	4 (25)
Hepatic	3 (43)	6 (67)	9 (56)
Musculoskeletal	4 (57)	9 (100)	13 (81)
Infectious disease	1 (14)	6 (67)	7 (44)
Time since hemophilia diagnosis — yr			
Mean (±SD)	29.9±8.1	40.6±10.0	35.9±10.5
Median (range)	34 (19–40)	36 (32–63)	36 (16–63)
Family history of neutralizing antibody to factor VIII — no. (%)			
Yes	3 (43)	0	3 (19)
No	2 (29)	6 (67)	8 (50)
Unknown	2 (29)	3 (33)	5 (31)
Bleeding episodes in ≤3 mo			
No. of episodes	5	9	14
Median (range)	1 (0–3)	1 (0–3)	1 (0–3)
Factor VIII regimen — no. (%)§			
Prophylaxis	6 (86)	9 (100)	15 (94)
On-demand	1 (14)	0	1 (6)

* Listed are data for patients who were assigned to receive recombinant factor VIII and BIVV001, which were administered sequentially to each patient at a dose of either 25 IU per kilogram or 65 IU per kilogram for each product. Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the patients, who could select more than one option.
‡ Classes of medical conditions include those that were present in at least one third of the patients in either group.
§ Listed is the most recent regimen that the patient was receiving before enrollment in the study.

BIVV001 owing to complications from a motor vehicle accident. Pharmacokinetic data for this patient were included in the calculation of pharmacokinetic measurements for recombinant factor VIII. Of the 9 patients who were enrolled in the higher-dose group, all 9 received both recom-

binant factor VIII and BIVV001. After the administration of BIVV001, the blood samples obtained from 1 patient in this group could not be evaluated for plasma factor VIII activity because of a sample-shipment error.

The patients in the two cohorts were all male and were primarily White (6 [86%] in the lower-dose group and 7 [78%] in the higher-dose group); the mean age was 33 years (range, 19 to 60) and 44 years (range, 32 to 63), respectively (Table 1). The mean (±SD) time since the diagnosis of hemophilia was 29.9±8.1 years in the lower-dose group and 40.6±10.0 years in the higher-dose group; the median number of bleeding episodes in the 3 months before screening was 1 (range, 0 to 3) in each group. All but 1 patient had received a prophylactic regimen immediately before entering this study.

SAFETY

All the patients were included in the safety analysis. No development of inhibitors to factor VIII was detected, and no hypersensitivity or anaphylaxis events were reported. In addition, no clinically relevant changes were detected in VWF activity or VWF antigen after the administration of BIVV001.

During the recombinant factor VIII treatment period, 8 adverse events were reported in 3 patients. These included 4 serious adverse events in 1 patient in the lower-dose group that were associated with a motor vehicle accident, after which the patient was withdrawn from the study before receiving BIVV001. During the receipt of recombinant factor VIII, the most common adverse event was an asymptomatic increase in the level of thrombin–antithrombin III complex (in 2 patients, 1 in each group). These 2 events were deemed by the investigator to be related to treatment, as was an increased fibrin D-dimer level in 1 of these patients; no associated clinical sequelae were reported in either patient (Table 2).

During the BIVV001 treatment period, 18 adverse events were reported in 9 patients. These events included a serious adverse event of a small-intestinal obstruction, which was attributed to complications from a prior appendectomy. The most common adverse events during the BIVV001 treatment period were an asymptomatic increase in the level of thrombin–antithrombin III complex and headache (in 2 patients each, 1 in each group). Of these events, the increased levels of thrombin–antithrombin III complex, which were reported in the same 2 patients who had these adverse events during the receipt of recombinant factor VIII, were deemed by the investigator to be related to BIVV001, as was the increased level of fibrin D-dimer. No associated clinical sequelae were reported.

PHARMACOKINETICS

Among the patients who received a single dose of recombinant factor VIII, the geometric mean half-life for plasma factor VIII activity was 9.1 hours (95% confidence interval [CI], 6.2 to 13.3) in the lower-dose group and 13.2 hours (95% CI, 10.9 to 15.9) in the higher-dose group, according to the one-stage assay. Among the patients who received BIVV001, the corresponding half-life was approximately four times as long in the lower-dose group (37.6 hours [95% CI, 33.3 to 42.5]) and more than three times as long in the higher-dose group (42.5 hours [95% CI, 39.7 to 45.6]) (Fig. 2 and Table S1). In the lower-dose group, the mean plasma factor VIII activity after injection of BIVV001 was 17% (range, 8 to 26) at 4 days and 5% (range, 2 to 10) at 7 days; in the higher-dose group, the corresponding plasma factor VIII activity was 51% (range, 35 to 72) at 4 days and 17% (range, 13 to 23) at 7 days (Fig. 2 and Table S1).

The area under the curve (AUC) for factor VIII activity over time was six to seven times as great as that for the same dose of recombinant factor VIII (4470 hours vs. 638 hours × IU per deciliter in the lower-dose group and 12,800 hours vs. 1960 hours × IU per deciliter in the higher-dose group). In the lower-dose group, the geometric mean clearance was 0.56 ml per hour per kilogram for BIVV001, as compared with 3.91 ml per hour per kilogram for recombinant factor VIII; the corresponding values were 0.51 ml and 3.31 ml per hour per kilogram in the higher-dose group.

After the administration of BIVV001, the geometric mean incremental recovery (i.e., the increase in plasma level per IU per kilogram of BIVV001 administered) was 2.7 IU per deciliter per IU per kilogram of BIVV001 (95% CI, 2.0 to 3.8) in the lower-dose group and 2.5 IU per deciliter per IU per kilogram of BIVV001 (95% CI, 2.2 to 2.8) in the higher-dose group. After the

Table 2. Safety Analysis.*

Adverse Event	25 IU/kg Group	65 IU/kg Group	All Patients
Recombinant factor VIII analysis			
Patients included in the analysis — no.	7	9	16
Patients with ≥1 adverse event — no. (%)	2 (29)	1 (11)	3 (19)
Adverse events — no.	6	2	8
Patients with ≥1 treatment-related adverse event — no. (%)†	1 (14)	1 (11)	2 (12)
Increased thrombin–antithrombin III complex	1 (14)	1 (11)	2 (12)
Increased fibrin D-dimer	0	1 (11)	1 (6)
Patients with ≥1 serious adverse event — no. (%)	1 (14)	0	1 (6)
Serious adverse events — no.‡	4	0	4
Forehead contusion	1	0	1
Hemarthrosis	1	0	1
Motor vehicle accident	1	0	1
Tendonitis	1	0	1
BIVV001 analysis			
Patients included in the analysis — no.	6§	9	15
Patients with ≥1 adverse event — no. (%)	3 (50)	6 (67)	9 (60)
Adverse events — no.	6	12	18
Patients with ≥1 treatment-related adverse event — no. (%)	1 (17)	1 (11)	2 (13)
Increased thrombin–antithrombin III complex	1 (17)	1 (11)	2 (13)
Increased fibrin D-dimer	0	1 (11)	1 (7)
Patients with ≥1 serious adverse event — no. (%)	1 (17)	0	1 (7)
Serious adverse events — no.	1	0	1
Small-intestine obstruction	1	0	1

* Adverse events were evaluated both during the period in which the patients received recombinant factor VIII and during the treatment period in which the patients received BIVV001.
† The investigators made the ruling as to whether an adverse event was related to the study product. No serious adverse events were deemed to be related to either recombinant factor VIII or BIVV001, and no patients discontinued the study because of an adverse event.
‡ The serious adverse events during the analysis period for recombinant factor VIII all occurred in one patient who was involved in a motor vehicle accident.
§ The patient who was involved in the motor vehicle accident was withdrawn from the study after receiving recombinant factor VIII but before receiving BIVV001.

administration of BIVV001, the geometric mean maximum factor VIII level was 70.1 IU per deciliter in the lower-dose group and 161.0 IU per deciliter in the higher-dose group, as compared with 51.8 IU per deciliter and 138.0 IU per deciliter, respectively, after the administration of recombinant factor VIII.

After the administration of BIVV001, similar trends in pharmacokinetic measurements were observed with the use of two-stage chromogenic assays, with a geometric mean half-life of factor VIII activity of 39.8 hours (95% CI, 32.5 to 48.9) in the lower-dose group and 45.8 hours (95% CI, 42.5 to 49.4) in the higher-dose group (Table S2).

DISCUSSION

Therapeutic goals for the treatment of hemophilia are expanding beyond a reduction in the annualized bleeding rate to include maintenance of joint health and improved quality of life for adults and children in all clinical situations. Ac-

cordingly, the prophylactic targets are being reevaluated as data have emerged that sustained factor VIII levels of more than the established standard of care (≥1%) are required to prevent all nontraumatic bleeding.

In a study involving 433 patients with mild or moderate hemophilia A, den Uijl et al. evaluated the association between plasma factor VIII activity and the number of episodes of bleeding in joints.[14] Their modeling showed a relative 18% reduction in bleeding frequency with every increase of 1 IU per deciliter in factor VIII activity. Patients with a factor VIII level of 10% or more had a very low risk of bleeding in joints, and those with a level of 15% or more had no risk. Soucie et al. also evaluated the relationship between factor VIII levels and bleeding in joints using longitudinal data from 3315 patients with nonsevere hemophilia A.[19] From their models, a factor VIII level of 15% predicted 1.4 episodes of bleeding per year in patients with hemophilia A. Thus, new single-agent treatments are focused more on achieving sustained, higher levels of factor VIII activity for longer periods of time and less on minimally acceptable trough levels.

BIVV001 was designed with novel mechanisms of protection from rapid plasma clearance and is one of a new class of factor VIII replacement products that break the VWF-imposed half-life ceiling.[29] BIVV001 protein engineering began with recombinant factor VIIIFc, a B-domain–deleted human factor VIII that is covalently linked to the Fc domain of human IgG1. Recombinant factor VIIIFc binds to neonatal Fc receptors and uses a naturally occurring recycling pathway. Fc neonatal receptors bind the Fc region of IgG1 and protect recombinant factor VIIIFc from intracellular degradation and thus extend its half-life in humans by a factor of approximately 1.5 to 1.7.[30] In BIVV001, a VWF–D′D3 domain was covalently linked to recombinant factor VIIIFc, which prevents recombinant factor VIIIFc from interacting with endogenous VWF, while maintaining the natural positive and negative regulatory mechanism of factor VIII. Thus, BIVV001 is a VWF-independent factor VIII product with a plasma half-life that is not subjected to VWF-mediated clearance. BIVV001 also includes two XTEN polypeptides, which are composed of natural hydrophilic amino acids. XTENs provide steric shielding and increase the hydrodynamic radius, consequently reducing clearance.[32] During the design of BIVV001, we also used computer modeling of immunogenicity prediction tools to assess major histocompatibility complex class II binding and to minimize the introduction of neoepitopes, thereby reducing the immunogenic potential.[29]

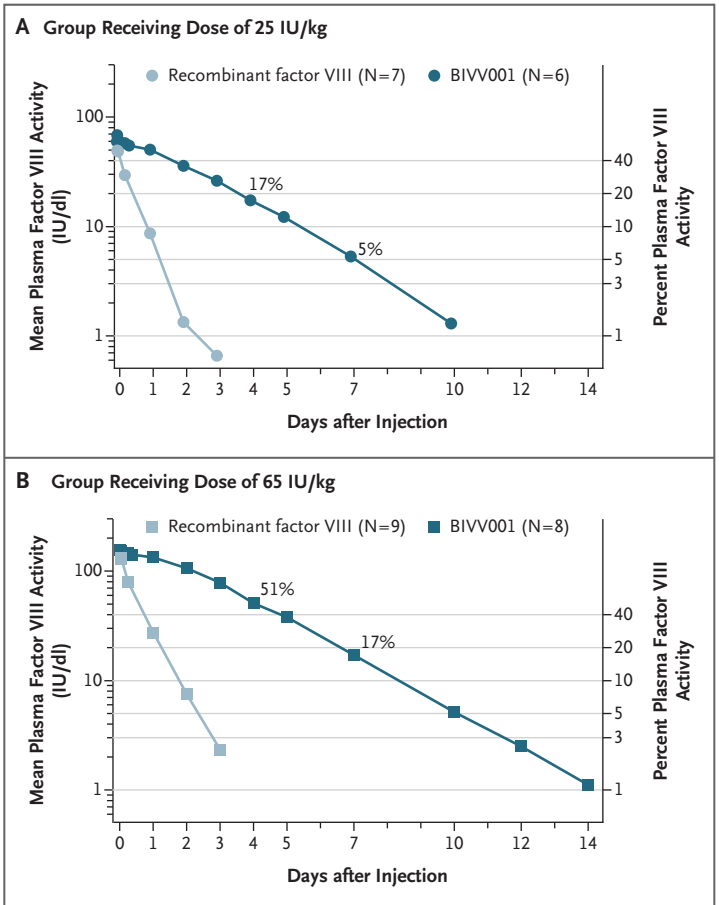

Figure 2. Factor VIII Activity at 14 Days in the Two Dose Groups.

Shown is the factor VIII activity among the patients who received an injection of recombinant factor VIII (followed by a 3-day washout period) and subsequently received an injection of BIVV001. Each of the two products was administered at a dose of 25 IU per kilogram (Panel A) or 65 IU per kilogram (Panel B). Factor VIII activity (as shown on a log scale on the left y axis) was determined with the use of a one-stage activated partial thromboplastin time–based clotting assay. The lower limit of quantification was 0.5 IU per deciliter for recombinant factor VIII and 1.0 IU per deciliter for BIVV001. For this analysis, values below the limit of quantification were treated as zero. The mean plasma factor VIII activity expressed as a percentage is shown on the right y axis. One patient who received recombinant factor VIII was withdrawn from the study following a motor vehicle accident before receiving BIVV001. Because of a sample-shipment error, one patient who received the two injections could not be evaluated for plasma factor VIII activity.

In this study, the administration of BIVV001 elicited a mean half-life of factor VIII activity that was three to four times as long as that of recombinant factor VIII and an AUC that was six to seven times as great. After a single dose of 65 IU per kilogram of BIVV001, the mean factor VIII activity was within the normal range at 4 days and 17% at day 7. These findings showed that BIVV001 could provide a high level of sustained factor VIII activity in patients with severe hemophilia A. Overall, single-dose BIVV001 elicited no safety concerns. The higher number of adverse events reported after BIVV001 treatment than after recombinant factor VIII treatment (18 events vs. 8 events) can probably be attributed, at least in part, to the longer duration of the safety observation period for BIVV001 (28 days vs. 3 or 4 days). The frequency and type of adverse events during BIVV001 treatment were similar in the low-dose and high-dose groups, and most events were assessed as being unrelated to the study product. Treatment-related adverse events included increased coagulation measurements after the administration of both recombinant factor VIII and BIVV001, with no corresponding clinical sequelae. Similar clinically insignificant laboratory abnormalities have been reported after exposure to another hemophilia product[35] and further support the hypothesis that this observation is secondary to the administration of procoagulant therapy. In nonclinical in vivo models of hemophilia, BIVV001 elicited four times the hemostatic control as that elicited by recombinant factor VIII, a finding that was consistent with the prolonged half-life of BIVV001.[29] The efficacy and safety of BIVV001 as a factor VIII replacement product, including the risk of inhibitor development, are being further evaluated in a phase 3 trial (ClinicalTrials.gov number, NCT04161495) involving previously treated patients with severe hemophilia A. Future evaluation of BIVV001 in previously untreated patients is anticipated.

Single-dose BIVV001 elicited no safety concerns in this small, early-phase study involving patients with severe hemophilia A. High levels of sustained factor VIII activity, which followed a normalization period after BIVV001 administration, have the potential to allow for better protection against all types of bleeding and a longer interval between administration of the product in patients with severe hemophilia A.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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