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First open-label, single-arm, prospective study of real-world use of FIX replacement therapy in a predominantly pediatric hemophilia B population in China

Renchi Yang, MD[a,*], Runhui Wu, MD, PhD[b], Jing Sun, MD[c], Feifei Sun, MD, PhD[d], Jeremy Rupon, MD, PhD[e], Francois Huard, MS, MBA[f], Joan M. Korth-Bradley, PharmD, PhD[e], Lihong Xu, MD[d], Binyu Luo, MD[d], Yingxue Cathy Liu, PhD[d], Pablo Rendo, MD[e]

Abstract

Background: Nonacog alfa (recombinant factor IX [FIX]) is approved in China for the control and prevention of bleeding events in patients with hemophilia B. This was the first study to assess prophylaxis and on-demand therapy with recombinant FIX replacement in a real-world setting in China. This study aimed to evaluate the safety and efficacy of nonacog alfa in Chinese patients with hemophilia B.

Methods: In this open-label, multicenter study (clinicaltrials.gov identifier NCT02336178), patients received on-demand or prophylactic treatment with intravenous nonacog alfa for approximately 6 months or 50 exposure days, whichever occurred first. The primary safety outcome was medically important events (i.e., development of FIX inhibitors, allergic reactions, and thrombotic events). Key secondary efficacy outcomes included the annualized bleeding rate for on-demand treatment and prophylaxis, response to on-demand treatment, the number of infusions per bleeding event, and the number of breakthrough bleeding events within 48 hours of prophylaxis.

Results: Seventy male patients (mean [standard deviation] age 7.8 [7.2] years) were enrolled (on-demand, n = 37; prophylaxis, n = 57 [24 patients were included in both groups]). Thirty-eight (54%) patients had up to 50 FIX exposure days before the study. The only medically important event was a transient low-titer FIX inhibitor (incidence 1.4%, 95% confidence interval, 0–7.7). The mean annualized bleeding rate was 26.3 for on-demand treatment and 6.5 for prophylaxis. A mean (standard deviation) of 1.5 (1.7) nonacog alfa infusions were given per bleeding episode; 78.8% of episodes resolved with 1 infusion. Response was "excellent" or "good" for 88% of the on-demand infusions. Twenty-three bleeding events (n = 11 patients) occurred within 48 hours of 2032 prophylaxis doses (1.13%).

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

[a] Institute of Haematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, [b] Hematology Oncology Centre, Beijing Children's Hospital, Capital Medical University, Beijing, [c] Nanfang Hospital, Southern Medical University, Guangzhou, [d] Pfizer (China) Research & Development Co, Ltd, Shanghai, China, [e] Pfizer Inc, Collegeville, PA, [f] Pfizer PIO, Paris, France.

[*] Correspondence: Renchi Yang, Institute of Haematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, China (e-mail: rcyang65@163.com).

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Conclusion: In the real-world setting, nonacog alfa is safe and effective for on-demand treatment and for prophylaxis for patients with hemophilia B in China.

Abbreviations: ABR = annualized bleeding rate, AE = adverse event, BU = Bethesda unit, CFDA = China Food and Drug Administration, CI = confidence interval, EDs = exposure days, FIX = factor IX, IU = international units, LETE = less-than-expected therapeutic effect, SAE = serious adverse event, SD = standard deviation, TEAE = treatment-emergent adverse event.

Keywords: BeneFIX, factor IX, hemorrhage, hypersensitivity, prevention, safety

1. Introduction

Hemophilia B is characterized by deficient or inactive factor IX (FIX) clotting factor, which can cause spontaneous or trauma-induced bleeding in joints and soft tissue.[1,2] Owing to its recessive X-linked nature, hemophilia B occurs primarily in males. Approximately 30% of patients have mild disease (>5% to <40% of normal FIX), about 33% have moderate disease (1%–5% of normal FIX), and about 37% have severe disease (<1% normal FIX).[3,4] In China, hemophilia B affects an estimated 0.5 per 100,000 individuals, amounting to approximately 7000 of nearly 1.4 billion people.[5] However, a large number of hemophilia cases in China are thought to be undiagnosed.[6]

Preferred care of patients with hemophilia B consists of FIX replacement using plasma-derived or recombinant FIX concentrates.[7–9] Management strategies include on-demand treatment of bleeding events and scheduled prophylactic infusions to reduce bleeding risk.[2,7,9] Nonacog alfa (BeneFIX; Pfizer Inc, Philadelphia, PA) is the only recombinant FIX replacement available in China, where most hemophilia B patients receive only on-demand treatment. Only about 1% of adults and 3% of children and adolescents with hemophilia A or B receive prophylaxis.[10]

Nonacog alfa is recombinant FIX produced in Chinese hamster ovary cells and is structurally and functionally comparable to endogenous FIX.[11] Initially approved in the United States in 1997,[11] the China Food and Drug Administration (CFDA) approved it in 2012 for the control and prevention of bleeding episodes and for use in the perioperative setting in patients with hemophilia B.[12] Licensure in China was based partially on an initial study of Chinese patients with previously treated hemophilia B (N=34) in which on-demand nonacog alfa produced excellent or good therapeutic response in 85% of hemorrhages at 8 hours after administration, with no new safety findings and no development of treatment-emergent FIX inhibitors, anaphylactic reactions, or thrombotic events.[13]

This study provides supplementary real-world safety and efficacy data in Chinese patients with hemophilia B treated with nonacog alfa in usual care settings, and is the first assessment of routine prophylaxis with recombinant FIX in the Chinese population.

2. Methods

2.1. Study design

This open-label, single-arm, multicenter, prospective, pragmatic study (clinicaltrials.gov identifier NCT02336178) was conducted at 16 hemophilia centers in China from 23 January 2015 to 22 August 2016 and was conducted post-approval to meet a CFDA requirement. Participants were treated with either on-demand or prophylactic intravenous infusions of nonacog alfa at the discretion of the treating physician. The dosage and frequency of treatment was determined by the treating physician in accordance with the nonacog alfa Chinese labelling. Patients were treated for approximately 6 months ± 7 days or 50 ± 5 exposure days (EDs), whichever occurred first. Nonacog alfa was prepared, reconstituted, and administered in accordance with Chinese label instructions.

The screening visit, which occurred within 28 days of initial treatment, included the collection of general and hemophilia history, physical examination, vital signs, and laboratory testing (hematology, serum chemistry, prothrombin time or international normalized ratio, FIX activity, recovery [optional], and inhibitor antibodies). This clinical evaluation was repeated at the end-of-study visit. Between visits, patients or their caregivers completed study diaries detailing adverse events (AEs), concomitant medications, characterization of bleeding episodes (site, traumatic/spontaneous), dose changes, and less-than-expected therapeutic effect (LETE). Throughout the study, patients kept infusion logs describing drug infusions given outside the study center, including date/time, international units (IUs) infused, reason for infusion, and rating of effectiveness of on-demand infusions. Inhibitor testing was performed locally at screening, first exposure, end of treatment, and otherwise at the investigator's discretion.

2.2. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and, where applicable, local regulations relevant to use of new therapeutic agents. Independent ethics committees at each study center approved the study protocol (see Supplemental Table S1, http://links.lww.com/MD2/A180 for listing of independent ethics committees). An external data monitoring committee, comprising physicians experienced in the management of hemophilia and a statistician, reviewed the data approximately every 6 months to ensure patient safety. Written informed consent was obtained from all patients or their parents or legal guardians.

2.3. Patient selection

In total, at least 60 patients with hemophilia B were planned for inclusion in the study. Males and females with hemophilia B of any severity were permitted to enroll if they were able to comply with study procedures and provide informed consent. As part of the commitment to the CFDA, we attempted to enroll different populations of Chinese patients with hemophilia B, including pediatric patients younger than 6 years, pediatric patients aged 6 to 12 years, previously untreated patients, patients receiving prophylaxis treatment after enrollment in the study, and patients with severe hemophilia B (FIX activity < 1%).

Individuals with bleeding disorders besides hemophilia B or with current or previous FIX inhibitor titer greater than the

laboratory's normal range or ≥0.6 Bethesda units [BU]/mL were excluded. Additional exclusion criteria included hypersensitivity to nonacog alfa, any excipient in the formulation, or Chinese hamster ovary cell proteins, and any condition that might serve as a contraindication or otherwise impair the patient's ability to comply with study procedures. Anyone who received investigational drugs within 30 days before study enrollment or during the study period and anyone who was a study site employee, employee's family member, or involved in the conduct of the study was excluded.

2.4. Safety

The primary safety end point was occurrence of medically important events (MIEs) consisting of the development of FIX inhibitors (titer exceeding testing laboratory's normal range or ≥0.6 BU/mL), allergic reactions, or thrombotic events; all MIEs were also reported as serious AEs (SAEs). Secondary safety outcomes included the frequency of AEs and SAEs. Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 19.0 and assessed for severity and relationship to treatment. Events were considered treatment-emergent if initial occurrence was on or after the first treatment day, or if it occurred previously but worsened during treatment.

2.5. Efficacy

Annualized bleeding rates (ABRs) were assessed in both the on-demand and prophylaxis groups. All bleeding episodes that occurred during the study were treated with on-demand nonacog alfa, with the number of infusions used to treat each bleeding event recorded. Response to on-demand treatment was assessed the same way in both treatment groups, using a 4-point scale (excellent, good, moderate, and no response; Supplemental Table S2, http://links.lww.com/MD2/A181),[13] and was included in an analysis of response to treatment. For patients receiving prophylaxis, an additional secondary efficacy end point included the number of spontaneous/nontraumatic breakthrough bleeding events within 48 hours of a nonacog alfa dose.

Additional secondary end points assessed for both groups included total FIX consumption (expressed in IUs), mean infusion dose (IU/infusion and IU/kg body weight), and incidence of LETE. In the on-demand setting, LETE was defined as 2 successive "no response" ratings after 2 successive on-demand nonacog alfa treatments within 24 hours of each other for the same bleeding event, without confounding factors. In the prophylaxis setting, LETE was defined as a spontaneous bleeding event within 48 hours after a regularly scheduled prophylaxis administration, with no confounding factors.

2.6. Statistical analysis

Three analysis populations were defined. The safety population comprised all patients who received at least 1 dose of nonacog alfa during the study. The on-demand population included all patients who participated in at least 1 day of an on-demand period, which was defined as the entire time of enrollment except time in any prophylaxis period. The prophylaxis population comprised all participants who received ≥1 prophylaxis dose. The prophylaxis period comprised the time from first prophylaxis infusion through 6 calendar days after the last prophylaxis infusion or the concluding day of the study, whichever was earlier. Patients who maintained a prophylaxis regimen throughout the study were not included in the on-demand population. Any period of ≥28 days without a prophylaxis infusion was considered a break in the prophylaxis period; such breaks were considered on-demand periods.

Descriptive statistics were calculated for all safety and efficacy end points. A 95% confidence interval (CI) was calculated for the incidence of patients who developed FIX inhibitors.

Each patient's ABR was calculated as: total number of all bleeding episodes during the on-demand period or the prophylaxis period/(number of days in the on-demand or prophylaxis period/365.25). For the purposes of ABR calculation, individual on-demand and prophylaxis periods were defined as the first day of treatment through the day before the start of the next treatment. In the ABR formula, the number of days in the treatment period in the denominator is the sum of time from all periods, and ABRs were calculated only if this sum was at least 14 days.

The incidence of LETE in the on-demand setting was calculated as number of bleeding events with LETE/number of bleeding episodes treated; bleeding episodes requiring on-demand treatment during a prophylaxis period were also included in this end point. The incidence of LETE in the prophylaxis setting was calculated as number of bleeding events with LETE/number of prophylaxis infusions.

FIX recovery was calculated as: (FIX activity collected at 15 minutes postdose [IU/dL] – pre-infusion FIX activity [IU/dL])/total dose (IU/kg). Although the formula specifies collection of FIX activity at 15 minutes, collections within 1 hour after infusion were accepted. If 2 pre-infusion FIX activity values were available, the lower of the 2 was used, and if pre-infusion FIX activity was less than 1, the value was set to zero.

3. Results

3.1. Patients

Of 77 patients screened, 70 were enrolled and treated (Fig. 1). The on-demand population included 37 patients, and the prophylaxis population included 57 patients. Twenty-four patients who alternated between on-demand and prophylaxis regimens were included in the respective analyses. Demographic and clinical characteristics are summarized in Table 1. All patients were Asian males with a mean age of 7.8 years and a mean body mass index of 17.3 kg/m^2. Of 70 patients, 30 were younger than 6 years, 31 were aged between 6 and 12 years, and 9 were older than 12 years.

3.2. Treatment exposure

The median number of exposure days was 43.5 (range, 3–54 days) for the entire study group (N = 70). Most patients (n = 43) had 29 to 60 exposure days. The median number of EDs was 8 in the on-demand population and 37 in the prophylaxis population.

3.3. Safety

A single MIE (the primary end point) occurred during the study: a 4-year-old patient developed a transient low-titer FIX inhibitor (0.7 BU/mL) after a total of 50 exposure days (on-study exposure day 25). Upon retesting approximately 1 month later, he had a negative result and the MIE was considered resolved. This patient

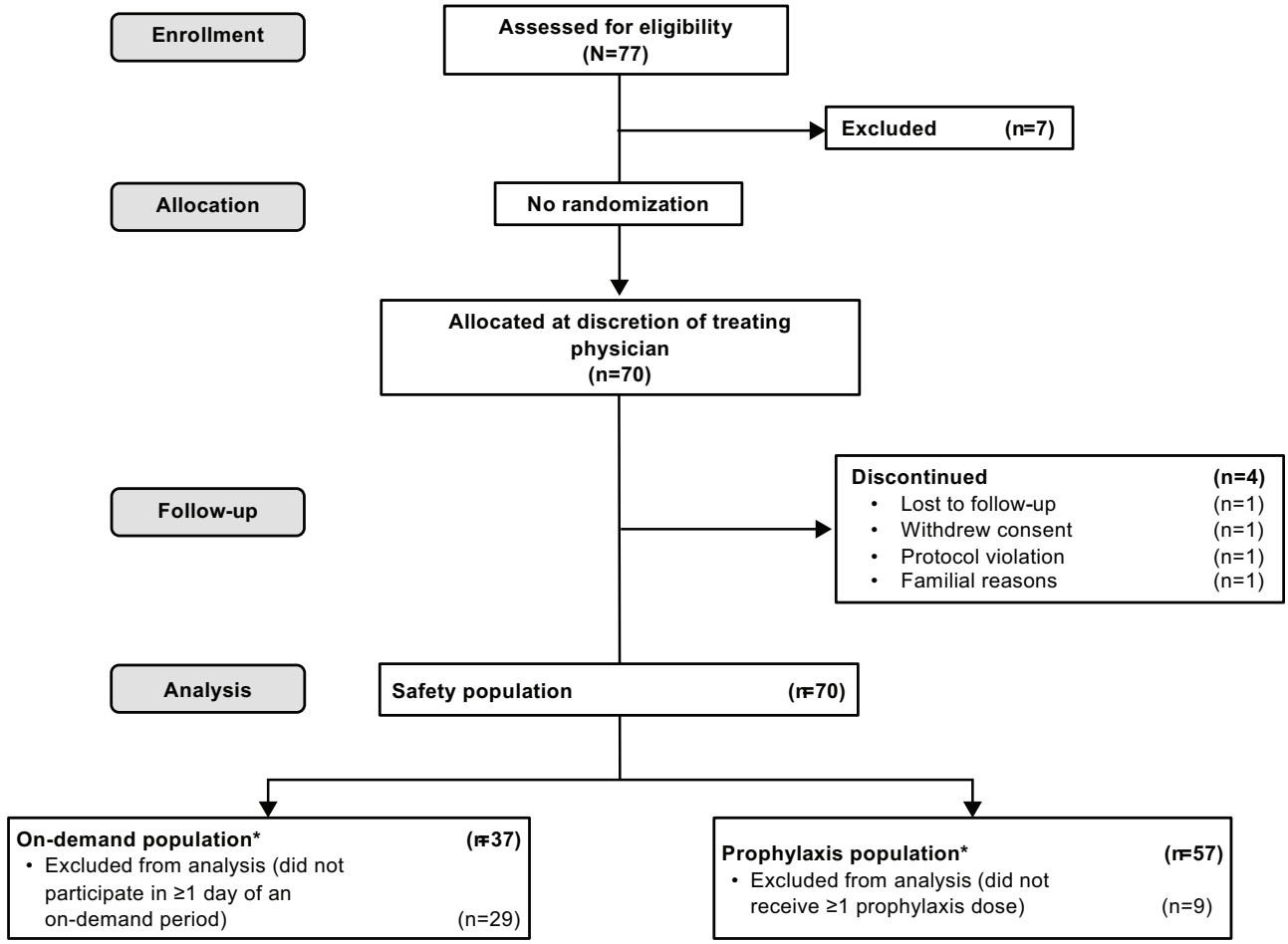

Figure 1. Patient disposition. *Patients who received at least 1 dose of on-demand or prophylactic treatment; 24 patients alternated between on-demand and prophylaxis regimens and were included in both groups.

Table 1

Demographics and baseline clinical characteristics (safety population).

Parameter	Patients (N = 70)
Age, mean (SD), yrs	7.8 (7.2)
<6, n (%)	30 (42.9)
6–12, n (%)	31 (44.3)
>12, n (%)	9 (12.9)
Sex, male, n (%)	70 (100)
Race, Asian, n (%)	70 (100)
Weight, mean (SD), kg	27.7 (18.1)
Height, mean (SD), cm	120.7 (28.4)
BMI, mean (SD), kg/m^2	17.3 (3.5)
Disease duration since diagnosis, mean (range), yrs	5.2 (0–28.6)
FIX activity at baseline, mean (range), %	1.5 (0.0–6.2)
Hemophilia severity, n (%)	
Mild (FIX activity >5–40%)	2 (2.9)
Moderate (FIX activity 1–5%)	30 (42.9)
Severe (FIX activity <1%)	38 (54.3)
Number (%) of prior exposure days to FIX products	
0	11 (15.7)
1–20	17 (24.3)
21–50	10 (14.3)
51–150	15 (21.4)
>150	17 (24.3)

BMI = body mass index, FIX = factor IX, SD = standard deviation.

had 25 documented EDs prior to study enrollment (prothrombin complex concentrate and fresh frozen plasma) and 25 total EDs to nonacog alfa during the study, before inhibitor development. The incidence (95% CI) of inhibitor development was therefore 1.4% (0–7.7) overall, 1.8% (0–9.4) during prophylaxis, and 0% (0–9.5) during on-demand treatment. No allergic reactions or thrombotic events occurred. The only other SAE was an oral hematoma in a 3-year-old boy whose parents had previously reduced his prophylaxis dosage from 33.3 IU/kg to 16.7 IU/kg once weekly.

During the study, 202 treatment-emergent adverse events (TEAEs) occurred among 62 patients (88.6%) (Supplemental Table S3, http://links.lww.com/MD2/A182). Individual TEAEs experienced by ≥2 patients are listed in Supplemental Table S4, http://links.lww.com/MD2/A183. Three AEs reported by 2 patients were considered treatment-related (the 1 case of FIX inhibitor development, and cough and rash in another patient, which were not considered to be allergic reactions to study medication). Six severe TEAEs were reported, including the 1 case of FIX inhibitor development, 1 case each of severe abdominal pain and pyrexia during on-demand treatment, and oral mucosa hematoma, viral upper respiratory tract infection, and arthralgia during prophylaxis. One patient had a dose reduction and 3 had temporary discontinuations owing to

TEAEs; no patients permanently discontinued the study due to an AE or died during the study.

3.4. Recovery

Recovery was assessed in 29 patients on day 1 of the study. The mean (standard deviation [SD]) was 0.67 (0.45) IU/dL/IU/kg (minimum, maximum: 0.14, 2.67).

3.5. Response to treatment of bleeding events

In the safety population (N = 70), 46 patients (65.7%) experienced bleeding events requiring on-demand treatment. Treatment response was rated "excellent" or "good" for 88% of 520 on-demand infusions (Table 2). Bleeding events were treated with a mean (SD) of 1.5 (1.7) nonacog alfa infusions, and the majority (78.8%) resolved with 1 infusion. The average infusion dose and total FIX consumption (IUs) are provided in Table 3.

3.6. Annualized bleeding rate

Among 37 patients in the on-demand population, 18 received treatment for bleeding episodes; the mean (SD) ABR in the on-demand group was 26.3 (23.1) (Table 4). The mean (SD) ABR for the prophylaxis group (n = 57) was 6.5 (9.1). Mean (SD) ABRs stratified by type and site of bleeding event are shown in Supplemental Table S5, http://links.lww.com/MD2/A184.

Table 2

Summary of on-demand treatment of bleeding events.

Parameter, n (%)	Patients (N = 70)
Patients with any treated bleeding event	46 (65.7)
Bleeding events resolved with 1 infusion	278 (78.8)
Response to all infusions	No. of infusions = 520
Excellent	254 (48.8)
Good	204 (39.2)
Moderate	54 (10.4)
No response	8 (1.5)

3.7. Incidence of LETE

No LETEs occurred in the on-demand setting. Overall, 2 confirmed incidents of LETE occurred in 2 pediatric patients with severe hemophilia in the prophylaxis group, for an overall incidence rate of 0.1% (95% CI, 0–0.4).

4. Discussion

This pragmatic study assessed prophylaxis as well as on-demand regimens of FIX replacement for patients with hemophilia B in China. This post-approval study provides further data on the safety and efficacy of this treatment in these patients in a real-world setting.

Similar to our previous study,[13] no new safety findings emerged in this study, supporting that nonacog alfa is safe to use in Chinese patients with hemophilia B. Of 70 patients treated with nonacog alfa, only 1 experienced an MIE, a transient low-titer FIX inhibitor. After the positive result, repeat testing was negative, and there was no evidence that the inhibitor was clinically significant. The overall incidence of inhibitor development was 1.4%. Safety findings were comparable to those recently reported in studies of patients with hemophilia B treated with nonacog alfa. In a study of 35 Chinese patients with hemophilia B treated with on-demand nonacog alfa, reported AEs were mostly mild to moderate, with no occurrence of treatment-emergent FIX inhibitor development.[13] Similarly, an analysis of pooled safety data from 6 prospective clinical studies of 412 patients with hemophilia B treated with prophylaxis and/or on-demand nonacog alfa demonstrated mostly mild to moderate AEs, with 5 occurrences of FIX inhibitor development

Table 3

Average infusion dose and total FIX consumption.

Parameter	No. of infusions	Infusion dose (IU)	Infusion dose by weight (IU/kg)	Total FIX consumption per patient (IU)
On-demand (n = 46)*				
Mean (SD)	11.3 (10.2)	731.6 (498.6)	24.5 (8.9)	9826.1 (14,816.3)
Median (range)	8.0 (1–44)	525.0 (200.0–2250.0)	23.0 (10.0–50.0)	4375.0 (250.0–65,000.0)
Prophylaxis (n = 57)				
Mean (SD)	35.6 (11.7)	540.1 (316.6)	23.5 (8.7)	19,224.1 (15,424.7)
Median (range)	37.0 (6–54)	500.0 (171.4–2250.0)	21.0 (10.3–51.2)	16,750.0 (4800.0–110,250.0)

FIX = factor IX, IU = international unit, SD = standard deviation.
* Includes 37 patients in the on-demand population plus an additional 9 patients from the prophylaxis group who required on-demand treatment for a bleeding episode.

Table 4

Annualized bleeding rate* in patients receiving on-demand treatment or prophylaxis with nonacog alfa.

	Annualized bleeding rate			
Population†	Mean	SD	Median	Range
On-demand (n = 18)‡	26.3	23.08	15.9	0–73.8
Prophylaxis (n = 57)	6.5	9.06	2.0	0–34.8

ABR = annualized bleeding rate, SD = standard deviation.
* Annualized bleeding rate = number of bleeding events in the on-demand or prophylaxis period/(number of days in the period/365.25).
† Some patients contributed to both the on-demand and prophylaxis analyses.
‡ ABR was calculated for the 18/37 patients in the on-demand group who received treatment with nonacog alfa for bleeding episodes during the on-demand period.

in 5 patients (1.2%), along with 15 allergic reactions and 2 occurrences of thrombosis (0.5%).[14]

The recovery observed in the young population participating in this study was similar to that reported by Hua et al[15] in a study of 4 Chinese boys aged 7 to 10 years, which was geometric mean (percent coefficient of variation) 0.78 (26) IU/dL/IU/kg.

Efficacy results provided support for use of nonacog alfa prophylaxis in pediatric patients in a real-world setting. There was a notable 4-fold decrease in ABR in the prophylaxis group compared with the on-demand group (mean 6.5 vs 26.3, respectively), and an LETE incidence of only 0.1% in the prophylaxis group. This result is consistent with findings from 2 prior studies with nonacog alfa that demonstrated a lower ABR with a prophylaxis versus on-demand regimen.[16,17] While the mean ABR during prophylaxis in this study was slightly higher compared with those studies, prophylaxis dosing along with overall study design differed between these studies, preventing direct comparisons of prophylactic ABRs. Notably, the mean prophylactic dose of nonacog alfa in this study was 23.5 IU/kg, which is at the low end of the range (13–78 IU/kg) used in the clinical trials that were reported in the product label.[12] There were a number of protocol violations considered potentially important (30 in 22 patients overall), which is likely because of the characteristics of the study design, reflecting the real-world care of hemophilia B patients in China. Ten prophylaxis patients received less factor than the range used in clinical trials reported in the product label, which may have contributed to some of the bleeding events in the prophylaxis group. Nonetheless, the results demonstrate for the first time in hemophilia B patients in China an improved ABR with prophylaxis compared with on-demand therapy in this real-world study population.

Efficacy of on-demand nonacog alfa was further supported by the high percentage (78.8%) of breakthrough/nontraumatic bleeding events that responded to the first on-demand nonacog alfa infusion, the favorable infusion response rating (88% excellent or good), and lack of LETE cases in the on-demand setting. These results are consistent with those of the previous study of nonacog alfa on-demand treatment in Chinese patients with hemophilia B, in which investigator assessments of response to treatment were "good" or "excellent" in about 85% of cases, and bleeding was treated with a mean of 1.2 infusions.[13] Our findings are also similar to those from a study of 34 patients with moderately severe to severe previously treated hemophilia B, in which 81.1% of bleeding episodes resolved with a single on-demand nonacog alfa infusion, and response to the first infusion was rated as "good" or "excellent" in 85.3% of episodes.[18]

Our study has several limitations. Although we attempted to enroll patients across a broad range of subgroups (e.g., <6 years of age, 6–12 years of age, previously untreated patients, and patients with severe disease), the overall small sample size (N = 70) and difficulty enrolling participants in some subgroups, especially previously untreated patients, prevented meaningful subgroup analyses. The entire study population comprised patients in China; caution should be used in extrapolating the observed results to patients with hemophilia B in other geographic locations and/or to patients of other ethnicities. Also, as this study assessed real-world usage of nonacog alfa in usual care settings, our analyses could not control for the potential impact of confounding factors, such as variations in clinical practice across different study sites, or of interventions and treatments other than nonacog alfa.

In conclusion, the results of this post-approval study conducted in a predominantly pediatric population in China demonstrated no new safety findings, with only 1 occurrence of an MIE (low-titer FIX inhibitor development) in 70 patients treated. These results, based on a real-world population, also support previously demonstrated efficacy and safety of nonacog alfa in treating Chinese patients with hemophilia B. This was the first study of FIX prophylaxis in China, and it provided initial clinical data supporting a marked reduction in bleeding events with the use of nonacog alfa prophylaxis in this population.

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Author contributions

Conceptualization: Renchi Yang, Feifei Sun, Francois Huard, Joan M. Korth-Bradley, Pablo Rendo.
Data curation: Renchi Yang, Runhui Wu, Jing Sun.
Formal analysis: Feifei Sun, Jeremy Rupon, Francois Huard, Joan M. Korth-Bradley, Binyu Luo, Yingxue Cathy Liu, Pablo Rendo.
Writing – original draft: Renchi Yang, Runhui Wu, Jing Sun, Feifei Sun, Jeremy Rupon, Francois Huard, Joan M. Korth-Bradley, Lihong Xu, Binyu Luo, Yingxue Cathy Liu, Pablo Rendo.
Writing – review & editing: Renchi Yang, Runhui Wu, Jing Sun, Feifei Sun, Jeremy Rupon, Francois Huard, Joan M. Korth-Bradley, Lihong Xu, Binyu Luo, Yingxue Cathy Liu, Pablo Rendo.

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