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ORIGINAL ARTICLE

Safety and efficacy of nonacog alfa for the treatment of haemophilia B in children younger than 6 years of age in a routine clinical care setting: the EUREKIX registry study

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ABSTRACT

Introduction: European regulatory authorities request postmarketing safety and efficacy data for factor IX (FIX) products.

Aim: Collect additional clinical data from routine nonacog alfa use in children aged <6 years with haemophilia B.

Methods: The EUREKIX registry included retrospective and prospective data collection phases. Safety was assessed via adverse drug reactions (ADRs)/adverse events (AEs) and events of special interest (ESIs) as the primary objective; efficacy was evaluated via annualised bleeding rates (ABRs).

Results: The retrospective phase comprised 37 subjects. Of these, 25 had severe haemophilia B. One subject experienced 2 ADRs; another experienced 4 ESIs of hypersensitivity. Median ABR in subjects receiving a predominantly on-demand regimen (prophylaxis <50% of time; n = 11) was 2.0; median ABR was 3.8 in those receiving predominantly prophylactic treatment (prophylaxis ≥50% of time; n = 24). Joint bleeding was infrequent (median ABR, 0.4; n = 35). The prospective phase included 26 subjects, with 17 continuing from the retrospective phase. A total of 20 subjects had severe haemophilia B. Three subjects experienced 7 treatment-related AEs; 3 experienced 4 ESIs. Median ABR was 4.5 and 1.1 in subjects who received predominantly on-demand (n = 5) or prophylactic treatment (n = 19), respectively; the overall median ABR for joint bleeding events was 0.0.

Conclusions: Overall, nonacog alfa treatment effectively controlled bleeding events, with no new safety signals identified. These data support the safety and efficacy of nonacog alfa in routine clinical settings in children aged <6 years.

KEYWORDS
Europe, factor IX, haematology, haemorrhage, observational study, paediatrics

1 | INTRODUCTION

Haemophilia B is an X-linked, monogenic bleeding disorder characterised by factor IX (FIX) deficiency that affects approximately 1 in 25 000 male births.[1] Severe haemophilia B, where FIX levels are less than 1% of normal, results in spontaneous bleeding occurring from a young age, most often as joint and muscle bleeding events in the absence of trauma.[2,3] Standard treatment for severe haemophilia is prophylactic replacement therapy, while moderate or mild haemophilia (FIX levels between 1% and 5% and >5% to 40%, respectively) is treated with either on-demand or prophylactic treatment.[2,4,5] In general, prophylaxis reduces the risk of arthropathies and may improve patients' quality of life.[6,7]

The human recombinant FIX, nonacog alfa, is a glycoprotein secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary cell line and is purified in a process that includes nanofiltration.[8,9] Treatment with nonacog alfa temporarily replaces the missing endogenous clotting FIX needed for effective haemostasis. Nonacog alfa is indicated for control and prophylaxis of bleeding episodes and for perioperative management in adult and paediatric patients with haemophilia B,[9] which is supported by data from clinical trials in mostly adolescents or adults with haemophilia B.[10-14] Overall, there is limited information on nonacog alfa use in young paediatric populations. One open-label, single-arm study in 25 children younger than 6 years with severe haemophilia B showed that 89% of on-demand bleeding episodes were resolved with 1 to 2 infusions of nonacog alfa; 1 subject developed a FIX inhibitor in relation to treatment, and, overall, a low incidence of treatment-related adverse events was reported.[15]

Regulatory authorities in Europe, such as the European Medicines Agency (EMA), increasingly request that sufficient and valid postmarketing safety and efficacy data be provided for FIX products.[16] Owing to the relatively small number of patients with haemophilia B, registries are a valuable tool to assess safety and efficacy in routine clinical settings. The EUropean REgistry in Kids Below Six Years of Age Treated with BeneFIX (EUREKIX) study was designed as a post-authorisation safety study (PASS) to collect further clinical data on routine nonacog alfa use in children younger than 6 years of age.

2 | MATERIALS AND METHODS

2.1 | Study design and ethics

This noninterventional, observational, multicentre, registry study was conducted at tertiary healthcare facilities in Italy, Spain, Sweden and the United Kingdom (EU PASS register number: ENCEPP/SDPP/3788) and included retrospective and prospective data collection phases. Investigational sites were recruited from a representative list of the country's centres in terms of size, care management system and practices. The study was conducted in accordance with the Good Pharmacoepidemiology Practices and with other research practice guidelines (eg ISPOR, PhRMA). Ethics committees at each study site approved the study protocol. Informed consent was obtained from at least 1 parent or guardian of each subject before data collection began.

Eligible subjects had a confirmed diagnosis of haemophilia B. For inclusion in the retrospective phase, subjects must have received treatment with nonacog alfa (BeneFIX; Pfizer) for at least 12 consecutive months before reaching age 6; at time of consent, these subjects would be, at most, 8 years of age. For the prospective phase, subjects able to accrue at least 12 months (up to 24 months) of nonacog alfa use before reaching 6 years of age were enrolled, with

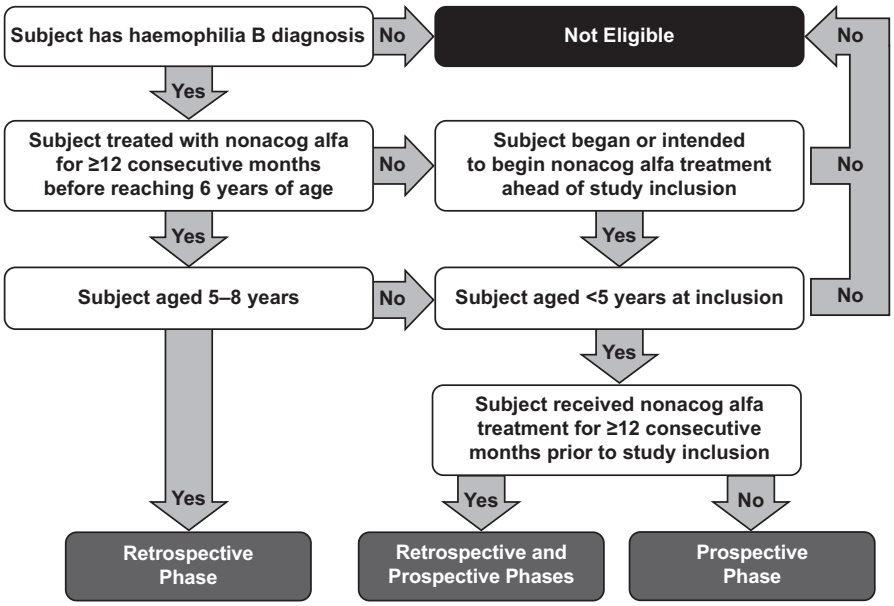

FIGURE 1 Study flow diagram

the decision to treat with nonacog alfa made before study entry. Subjects in the retrospective phase were able to continue to the prospective phase if they satisfied the inclusion criteria. Treatment of haemophilia B with a product other than nonacog alfa was exclusionary in both phases. Figure 1 outlines entry requirements for each study phase.

Patient records and treatment diaries from routine clinical practice served as sources for data collection; as this was a noninterventional study, no additional visits were made nor procedures performed. The following were collected during review: demographics, disease/treatment history, school attendance, FIX dosing, FIX mutation and FIX recovery (if available). The dosage of nonacog alfa was based on the approved Summary of Product Characteristics [8] and was adjusted solely according to medical and therapeutic necessity by the treating physician.

The primary study objective was to assess safety outcomes, which were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) definitions of system organ class and preferred terms. In the retrospective phase, adverse events (AEs) were described as adverse drug reactions (ADRs) because only AEs related to nonacog alfa treatment were collected. In the prospective phase, AEs that occurred during treatment with nonacog alfa were collected and referred to as treatment-emergent adverse events (TEAEs), but these could be related or unrelated to nonacog alfa treatment. Other safety variables assessed included serious ADRs in the retrospective phase, serious TEAEs in the prospective phase and events of special interest (ESIs) in both phases (ie FIX inhibitor development, allergic-type hypersensitivity reaction, thrombotic events, red blood cell agglutination in tubing or syringe, and low recovery).

TABLE 1 Demographics and baseline disease characteristics

Parameter	Retrospective Phase FAS Population (n = 37)	Prospective Phase FAS Population (n = 26)
Age, mean (SD), years	5.0 (2.1)	2.5 (1.1)
Age, range, years	2.0–8.7	0.3–4.7
Sex, male, n	37	26
Race, white, n	34	23
Age at diagnosis, mean (SD), years	0.5 (0.7)	0.4 (0.4)
Age at first bleeding event, mean (SD), years	0.8 (0.8)	0.6 (0.4)
Time on study by phase, mean (SD), years	3.4 (1.4)	1.5 (0.6)
Family history of haemophilia B, n	25	16
Severity of haemophilia B, n		
Mild (FIX:C > 5 to 40 IU/dL)	4	1
Moderate (FIX:C 1 to 5 IU/dL)	8	5
Severe (FIX:C < 1 IU/dL)	25	20
History of inhibitor, n	2[a]	2[b]
Nonacog alfa as first treatment for haemophilia B, n	32	23
Age at first exposure to nonacog alfa, mean (SD), years	1.1 (0.8)	0.9 (0.7)
FIX genetic mutation, n	28	22
Nonsense, n	1	4
Missense, n	14	8
Insertion, n	0	1
Deletion, n	3[c]	3[d]
Other, n	10[e]	6[f]

Abbreviations: FAS, full analysis set; FIX:C, factor IX activity; SD, standard deviation.

[a]One subject had a nonsense mutation and one had a deletion, c.571delC (p.Arg191Val fs*12).

[b]Both subjects had nonsense mutations.

[c]Deletions were as follows, n = 1 each: not specified; c.657_660delATCA (p.Gln219His fs*25); and c.571delC (p.Arg191Val fs X12).

[d]Deletions were as follows, n = 1 each: not specified; g.5118-5121delGTTT; and c.657_660delATCA (p.Gln219His fs*25).

[e]Included the following, n = 1 each unless noted: K02402(F9_001):c.529C>A (p.Pro177THR) (n = 2); nucleotides changes 30957 T > C in exon 8; substitution exon 2; p.Asp405Gly; p.Arg252Stop; p. E294 fs; p.R384X; pathogenic mutation in exon 8; hemizygous for the c.252+3G>C mutation.

[f]Included the following, n = 1 each: K02402(F9_001):c.529C>A (p.Pro177THR); p.Gly106Ser (c.316G>A); substitution exon 2; p.Asp405Gly; p. E294 fs; p.R384X.

Efficacy was characterised as a secondary study objective by assessing annualised bleeding rates (ABR) and the following investigator-reported outcomes: response to nonacog alfa treatment, incidence of less-than-expected therapeutic effect (LETE) and lack of effect. Treatment groups were defined as follows: predominantly prophylaxis, received prophylactic treatment ≥50% of the time; predominantly on-demand, received prophylaxis <50% of the time. Impacts on daily living were collected during the prospective phase only (2–4 times per year) and included total number of unplanned days of missed work for parents/caregivers and total number of days subject's daily activities were affected by disease.

Target joints were defined as joints in which 3 or more spontaneous bleeding events had occurred during the previous 6 months.[7] Each subject's response to treatment was rated using a 4-point scale (excellent, good, moderate or no response); ratings were based on time to bleeding event resolution (pain relief and/or improvement in signs of bleeding) and whether an additional infusion was required for resolution of the bleeding event. The designation of LETE applied if the following circumstances occurred: (1) no response to treatment of bleeding events during on-demand treatment (ie 2 consecutive 'no response' ratings given to consecutive nonacog alfa infusions given up to 24 hours apart for the same bleeding event), (2) occurrence of a bleeding event during prophylaxis (ie a spontaneous bleeding episode within 48 hours following a regularly scheduled dose of nonacog alfa) or (3) lower than expected recovery. Lack of effect referred to infusions with failed pharmacologic action or no therapeutic benefit.

2.2 | Sample size and statistical analysis

The study was designed to enrol approximately 50 subjects in total across both treatment phases. The full analysis set (FAS) for retrospective data included all subjects with at least 12 months of data in the retrospective phase; the FAS for prospective data included all subjects with at least 1 postbaseline visit in the prospective phase. Subjects who underwent immune tolerance induction (ITI) were excluded from the FAS for efficacy analyses because patients with haemophilia B and an FIX inhibitor are a distinct population. The decision to exclude these subjects was made at the point of data analysis. The safety population comprised all enrolled subjects who received at least 1 dose of nonacog alfa.

Descriptive statistics were used to summarise each study phase; no inferential comparisons were made between study phases. For continuous variables, the following calculations were performed: number of observations, mean plus 95% confidence interval (CI) or standard deviation (SD), and median, minimum, and maximum values. Categorical variables were described in terms of frequencies. For proportions with 95% CI specified, the CI was 2-sided, with an alpha level of 0.05. Statistical analyses were conducted using SAS version 9.2 (SAS Institute).

An administrative data collection cut-off date of 31 July 2016 was enacted once the retrospective phase had been completed and once the prospective phase had been completed for the majority of subjects in the study. For this reason, some subjects in the prospective phase had less than 12 months of accrued data.

3 | RESULTS

Forty-eight paediatric subjects were screened for inclusion; 46 met the eligibility criteria and were enrolled (Figure 2). At study entry, 37 subjects had been treated with nonacog alfa for at least 12 months before reaching 6 years of age. Of these, 20 subjects were aged 5 to 8 years at the time of data collection and were included in the retrospective phase only. Subjects younger than 5 years at entry into the retrospective phase were also enrolled in the prospective phase (n = 17). An additional 9 subjects younger than 5 years at time of study entry who began or intended to begin nonacog alfa for at least 12 months were enrolled in the prospective phase.

3.1 | Retrospective phase

The retrospective phase enrolled 37 subjects (Figure 2); the mean (range) duration of data collection was 3.4 (1–6) years. Table 1 shows the subjects' demographic characteristics. Nearly all subjects had moderate or severe haemophilia B (33/37). Although more than half of the subjects experienced at least 1 joint bleeding event (56.8% [21/37]), no subject had a target joint.

3.1.1 | Safety

In the retrospective phase safety population (n = 37), 2 ADRs (ecchymosis and skin haemorrhage) considered related to nonacog alfa treatment were recorded in 1 subject (Table 2). Both were of mild severity and resolved by the end of the study phase; no serious ADRs were reported. Four serious treatment-related ESIs occurred in 1 subject; this subject experienced hypersensitivity of mild severity on all 4 occasions. No action was taken for the hypersensitivity ESIs, and all resolved by the end of the study phase. No deaths occurred during the retrospective phase, and no subject experienced an ADR or ESI that led to permanent treatment discontinuation.

3.1.2 | Efficacy

Thirty-five subjects contributed data to the efficacy analyses, excluding 2 subjects with a history of an FIX inhibitor who received an ITI regimen. The mean (SD) dose of nonacog alfa used by subjects receiving predominantly prophylaxis treatment (n = 24) was 683.5 IU (260.3); the median dose (range) was 601.0 IU (396.6–1277.5). The

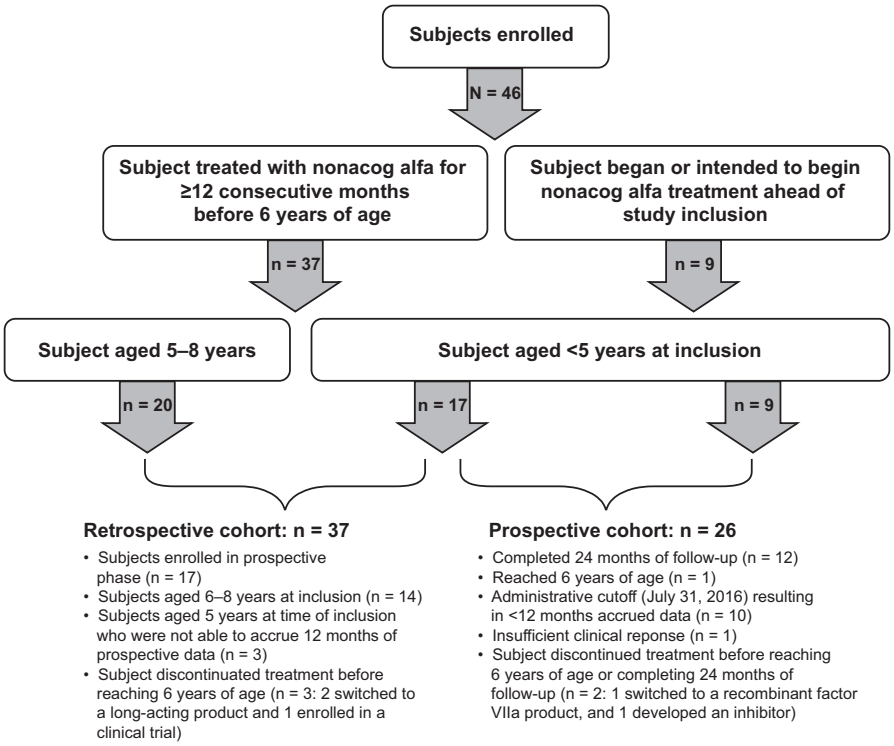

FIGURE 2 Subject disposition

TABLE 2 Overview of safety results[a]

Parameter	Retrospective phase SAS population (n = 37)	Prospective Phase SAS population (n = 26)
Subjects with ADRs/TEAEs, n	1	19
Number of ADRs/TEAEs	2	52
Treatment-related events	2	7
Subjects with serious ADRs/TEAEs, n	0	14
Number of serious ADRs/TEAEs	0	25
Number of severe serious ADRs/TEAEs	0	5
Subjects with ESIs (all serious), n	1	3
Number of ESIs during the data collection period	4	4
Development of factor IX inhibitor	0	1[b]
Hypersensitivity	4	3[c]
Subjects with ESIs leading to permanent treatment discontinuation, n	0	2

Abbreviations: ADR, adverse drug reaction; AE, adverse event; ESI, event of special interest; SAS, safety analysis set; TEAE, treatment-emergent adverse event;.

[a]In the retrospective phase, AEs were described as ADRs, as only AEs related to treatment were collected; in the prospective phase, AEs were described as TEAEs; these could be related or unrelated to nonacog alfa treatment.

[b]This subject experienced 1 instance of factor IX inhibitor development; this event resulted in permanent discontinuation of nonacog alfa treatment.

[c]One subject experienced 2 instances of hypersensitivity.

mean (range) dosing interval for subjects receiving prophylaxis in the retrospective phase was 3.8 (1.1–14.1) days. For those using predominantly on-demand treatment (n = 11), the mean (SD) dose of nonacog alfa was 789.9 IU (307.5), and the median dose (range) was 750.0 IU (480.0–1539.2). During the retrospective phase, median (range) ABR for all bleeding events was 2.5 (0.0–11.4). Annualised bleeding rates by predominant regimen, bleeding event type (traumatic or spontaneous), and location (joint, soft tissue/muscle, or central nervous system [CNS] bleeding events) for all subjects are presented in Table 3.

TABLE 3 Annualised bleeding rates, response to treatment, and other efficacy outcomes

Parameter	Retrospective phase (N = 35)[a]	Prospective phase (N = 24)[a]
Subjects by treatment type, n		
Predominantly[b] prophylaxis regimen	24	19
Predominantly[b] on-demand regimen	11	5
ABR, mean (95% CI)		
All bleeding events	3.4 (2.5, 4.4)	2.9 (0.9, 5.0)
Predominantly[b] prophylaxis regimen	3.7 (2.7, 4.7)	2.9 (0.3, 5.4)
Predominantly[b] on-demand regimen	3.0 (0.8, 5.1)	3.3 (0.0, 6.8)
Spontaneous bleeding events	0.5 (0.3, 0.7)	0.5 (0.1, 1.0)
Traumatic bleeding events	2.2 (1.5, 2.9)	2.2 (0.3, 4.2)
Joint bleeding events	0.6 (0.4, 0.8)	0.4 (0.1, 0.8)
Soft tissue/muscle bleeding events	1.1 (0.6, 1.6)	0.9 (0.2, 1.7)
CNS bleeding events	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)
ABR, median (range)		
All bleeding events	2.5 (0.0–11.4)	1.3 (0.0–22.4)
Predominantly[b] prophylaxis regimen	3.8 (0.0–8.1)	1.1 (0.0–22.4)
Predominantly[b] on-demand regimen	2.0 (0.0–11.4)	4.5 (0.0–6.2)
Spontaneous bleeding events	0.3 (0.0–1.9)	0.0 (0.0–4.4)
Traumatic bleeding events	1.4 (0.0–7.5)	0.5 (0.0–22.4)
Joint bleeding events	0.4 (0.0–2.8)	0.0 (0.0–2.7)
Soft tissue/muscle bleeding events	0.6 (0.0–6.4)	0.3 (0.0–7.5)
CNS bleeding events	0.0 (0.0–1.0)	0.0 (0.0–0.5)
Best response to treatment rated as 'excellent' or 'good', n		
Overall	34	16
Predominantly[b] prophylaxis regimen	24	12
Predominantly[b] on-demand regimen	10	4
Less-than-expected therapeutic effect, n	1	0
Lack of effect, n	2	0
FIX recovery, IU/dL per IU/kg of nonacog alfa, mean (95% CI)[c,d]	1.4 (0.0, 3.0)	0.5 (0.2, 0.8)

Abbreviations: CI, confidence interval; CNS, central nervous system; FAS, full analysis set; FIX, factor IX.

[a]Two subjects were excluded from the efficacy analysis of both the retrospective and prospective phases because they had received an immune tolerance induction regimen. In the retrospective phase, both subjects had a history of FIX inhibitor related to nonacog alfa. The first subject had received nonacog alfa 500 IU as prophylaxis every other day for more than a year when inhibitor developed, and had a peak recorded titre of 2.2 Bethesda units in the retrospective phase. For the second subject, nonacog alfa treatment details prior to inhibitor development were not available, but the subject's peak recorded titre was 4.5 Bethesda units in the retrospective phase and 25 Bethesda units in the prospective phase.

[b]Predominantly prophylaxis: received prophylactic treatment ≥50% of the time in a study phase; predominantly on-demand: received prophylaxis <50% of the time in a study phase.

[c]Based on available responses: retrospective phase (n = 20); prospective phase (n = 17).

[d]There was no central study laboratory.

The overall response to treatment with nonacog alfa was rated as excellent or good for 34/35 subjects with an available evaluation; all available responses to nonacog alfa by treatment group (predominantly on-demand vs predominantly prophylaxis) were also rated favourably. One subject experienced an LETE during the retrospective phase in which a spontaneous bleeding event occurred within 48 hours of a regularly scheduled prophylaxis dose. Three events of mild lack of effect were documented in 2 subjects; of these, 2 events were considered related to treatment. In all 3 events, the dose of the study drug was increased, and no further adjustments to treatment were required.

3.2 | Prospective phase

The prospective phase enrolled 26 subjects (Figure 2); the mean (range) duration of data collection was 1.5 years (0.4–2.2). Subject demographics and baseline disease characteristics are summarised

in Table 1. Nearly all subjects had moderate or severe haemophilia B (25/26). Among subjects with an available response (n = 24), 12 (50%) experienced at least 1 joint bleeding event; no subject had a target joint.

3.2.1 | Safety

In the prospective phase safety population (n = 26), 52 TEAEs were recorded in 19 subjects. Seven TEAEs (cyanosis, fatigue, nephrotic syndrome, cough, erythema, blister and flushing) experienced by 3 subjects were considered related to nonacog alfa treatment. The most common TEAEs were head injury (n = 9), pyrexia (n = 4) and anaemia (n = 2). Fourteen subjects reported 25 serious TEAEs; the most common was head injury (n = 6). Dose increases were reported for 7 subjects following serious TEAEs of contusion, excoriation, head injury (in 4 subjects), peripheral oedema, mouth haemorrhage and tongue haemorrhage. Four serious treatment-related ESIs occurred in 3 subjects, including 1 event of a high-titre FIX inhibitor in 1 subject and 3 events of hypersensitivity in 2 subjects, which resolved by the end of the study phase (1 severe, 1 mild and 1 of unknown severity; 2 events occurred in 1 subject). Treatment with nonacog alfa was discontinued in the subject who experienced an ESI of a high-titre inhibitor; no action was taken for the hypersensitivity ESIs.

Three subjects discontinued treatment because of serious TEAEs, of which 2 were ESIs. One subject with an unspecified deletion mutation who was enrolled in the prospective phase developed a cough, head injury, flushing and fatigue (all of mild severity) and a high-titre FIX inhibitor. FIX inhibitor development began after the subject received 12 infusions of nonacog alfa as part of a predominantly on-demand regimen (first positive antibody titre was 16.3 Bethesda units (BU), and, approximately 3 weeks later, titre was 9.7 BU; the event of development of an FIX inhibitor was not resolved at end of study). Nonacog alfa treatment was discontinued, but the subject remained in the study for an additional 8 months (1.3 years total). A second subject, after 2 years in the retrospective phase, enrolled in the prospective phase and developed nephrotic syndrome (moderate severity), which led to discontinuation after 1.1 years on study; the subject had received both on-demand and prophylaxis regimens. A third subject who received prophylaxis treatment and was enrolled only in the prospective phase discontinued after experiencing hypersensitivity, erythema and blisters (all of unknown severity) after 0.4 years on study. No deaths occurred during the prospective phase.

Overall, the subject who developed a FIX inhibitor on study (prospective phase) represented the only case of inhibitor formation across all unique subjects (1/46). In total, 7 events of hypersensitivity occurred in 2 unique subjects (1 subject experienced 5 hypersensitivity events [4 in the retrospective phase; 1 in the prospective phase]; another experienced 2 hypersensitivity events [prospective phase]). Only 1 case of nephrotic syndrome was reported across the entire study (also in the subject with 5 hypersensitivity reactions).

3.2.2 | Efficacy

Twenty-four subjects contributed data to the efficacy analyses, excluding 2 with a history of an inhibitor who received an ITI regimen. The mean (SD) dose of nonacog alfa used by subjects receiving predominantly prophylaxis (n = 19) was 712.9 (223.5) IU; the median (range) dose was 697.1 IU (249.1–116.7). The mean (range) dosing interval for subjects receiving prophylaxis in the prospective phase was 4.4 (1.7–22.5) days. For those using a predominantly on-demand treatment regimen (available responses, n = 4), the mean (SD) dose of nonacog alfa was 578.5 (87.2) IU, and the median (range) dose was 612.5 IU (450.0–638.9). During the prospective phase, median (range) ABR for all bleeding events was 1.3 (0.0–22.4). Annualised bleeding rates by predominant regimen, bleeding event type (traumatic or spontaneous) and location (joint, soft tissue/muscle or CNS bleeding events) for all subjects are presented in Table 3.

The overall response to treatment with nonacog alfa was rated as excellent for all 16 subjects with an available evaluation; all available responses to nonacog alfa by treatment group (predominantly on-demand vs predominantly prophylaxis) were also rated favourably. No LETE or lack of effect events were reported for subjects in the prospective phase. In terms of available daily impact variables (ie which were recorded during routine clinical practice), the mean number (range) of unplanned days missed from work by parents/caregivers (n = 10) was 0.6 days (0.0–5.0) during the prospective phase. Subjects (n = 9) experienced a mean (range) of 0.8 days (0.0–5.0) days where their daily activities were affected by their disease during the prospective phase.

4 | DISCUSSION

In this noninterventional registry of routine nonacog alfa use in paediatric haemophilia B subjects younger than 6 years, safety events related to nonacog alfa included 2 ADRs (both in 1 subject) and 4 ESIs of hypersensitivity (all in 1 subject) in the retrospective phase. Drug-related safety events in the prospective phase included 7 TEAEs in 3 subjects and 4 ESIs in 3 subjects (hypersensitivity, n = 2, with 1 subject experiencing 2 occurrences, and an FIX inhibitor, n = 1). All subjects with hypersensitivity reactions during either study phase had a history of FIX inhibitor before the data collection period began. Overall, treatment-related adverse events in either phase were consistent with other reports on nonacog alfa use, and no new safety concerns were detected.[8,10,12,13,15,17]

In both study phases, most subjects used predominantly prophylaxis treatment. The ABR in the retrospective phase was comparable to that reported in a prior study of nonacog alfa in children younger than 6 years with severe haemophilia who received prophylaxis in routine practice (ABR: 3.7, N = 22)[15]; the ABR with predominantly prophylaxis treatment in the prospective phase was similar to that reported with an extended half-life product in children younger than 6 years with moderate to severe haemophilia B (median ABR, 1.1; N = 15).[18] Additionally, overall ABRs in this study were consistent

with ABRs reported in a recent retrospective analysis of adult and paediatric subjects with moderate to severe haemophilia B who received prophylaxis (ABR range, 1.7–8.5).[19] Because subjects in this study could transition between prophylaxis and on-demand regimens, there were smaller differences in median ABRs between treatment regimens in each phase compared with previous studies of nonacog alfa for haemophilia B treatment.[14,17] In addition, this could partially explain the finding of a lower median ABR with predominantly on-demand versus predominantly prophylactic treatment in the retrospective phase.

In both study phases, response to treatment was positively rated for nearly all infusions, similar to findings in prior nonacog alfa studies in adults and children.[15,17,20] In this study, 3 events of lack of effect were reported (all of which resolved with dose increases). While no LETEs were observed with on-demand or prophylaxis treatment in a study of adolescents and adults with moderate to severe haemophilia B,[17] this discrepancy may be explained by differences in pharmacokinetics and drug metabolism between children and adults (ie children may require more frequent dosing or higher doses to achieve therapeutic effects).[8,15,21,22] The observed FIX recovery in the prospective phase may be related to the mean age of subjects in this cohort. Results from previous studies with recombinant FIX indicate that younger patients may have lower recovery and that recovery increases with age.[21,23]

During the prospective phase of this study, parents/caregivers and subjects reported low impacts for unplanned days missed from work and for effect on daily activities. One previous study reported an average of 11 unplanned days missed from work (over a period of 229 days) for 19 caregivers of patients with haemophilia.[24] Possible explanations for fewer missed workdays for caregivers in the current study include frequency of data collection (2–4 times/year here vs daily diaries in the previous study) or differences in disease severity (subjects without an inhibitor here vs subjects with an inhibitor in the previous study). There may be other aspects of disease burden for both caregivers (eg negative impact on work, anxiety) and subjects (eg pain, impaired quality of life) that were not captured by the impact measures in the current study.[25,26]

In this study, approximately half of subjects in both data collection phases had at least 1 joint bleeding event over an average of 3.4 years in the retrospective phase and 1.5 years in the prospective phase; however, none had target joints. Nonacog alfa treatment was associated with low joint bleed ABRs throughout the study, similar to another study of children younger than 6 years with haemophilia B receiving nonacog alfa prophylaxis.[15] These results suggest that nonacog alfa effectively maintains a low incidence of clinically apparent joint bleeding events in young children, which has long-term implications for joint disease[27] and may allow them to lead more active social lives.[28]

These findings should be viewed with several limitations in mind. During the retrospective phase, safety and efficacy data were based on medical history; thus, data collection was limited by available information. In the prospective phase, the complexity of data collection during routine clinical management may have increased the number of subjects lost to follow-up. To minimise this bias, data from both data collection phases were analysed separately. These findings may also be limited by selection bias owing to the voluntary participation of study investigators and to subject selection; this bias was reduced by investigators attempting to systematically enrol subjects in the registry. Finally, despite wide eligibility criteria, most included subjects were white with moderate to severe haemophilia B; thus, these results may not be broadly generalisable to other races or ethnic groups in countries with different treatment capabilities or healthcare systems.

5 | CONCLUSIONS

In this 2-part registry of children younger than 6 years with haemophilia B, no new safety concerns were reported with routine nonacog alfa use. In addition, nonacog alfa effectively controlled bleeding events, as demonstrated by low ABRs and favourable responses to treatment. The EUREKIX registry adds valuable information on nonacog alfa use as a FIX replacement strategy in children younger than 6 years of age in routine clinical practice.

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CONFLICT OF INTEREST

This study was sponsored by Pfizer. R. Liesner has received travel support and served as a speaker and consultant for Bayer, CSL Behring, Grifols, NovoNordisk, Octapharma, Roche, Shire and Sobi. N.G. Andersson has served as a speaker and/or on advisory boards for Bayer, CSL Behring, Octapharma and Sobi. T. Frisk has served as a speaker and/or consultant and/or attended advisory boards for Bayer, CSL Behring, Novo Nordisk, Octapharma, Roche and Sobi. E. Santagostino has received travel support and served as a speaker and consultant for Bayer, Bioverativ, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, Sobi, Spark and Uniqure. M. Schulz and L. Young are employees of Pfizer and may own stock/options in the company. P. Giordano has no disclosures to report. A. Tagliaferri has served on advisory boards for Bayer, Novo Nordisk and Roche. No author received an honorarium related to the development of this manuscript.

AUTHOR CONTRIBUTIONS

Ri Liesner served as principal investigator. Elena Santagostino served as a study investigator. Nadine G Andersson served as a country coordinating investigator. Ri Liesner, Nadine G Andersson and Elena Santagostino enrolled patients and participated in the collection and assembly of data. All authors had full access to the data and contributed to the drafting, critical review, and revision of the manuscript. All authors granted approval of the final manuscript for submission.

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