

A national French noninterventional study to assess the long-term safety and efficacy of reformulated nonacog alfa

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BACKGROUND: Nonacog alfa, the recombinant Factor IX (F IX) used for the treatment of hemophilia B, was approved in Europe in 1998. A reformulated version was approved for European use in 2007.

STUDY DESIGN AND METHODS: This postmarketing study, as recommended by the risk management plan, was conducted to confirm the safety of reformulated nonacog alfa in a usual care setting in France. This open-label, noninterventional, prospective, longitudinal postmarketing study comprised 19 French hemophilia centers. Patients with hemophilia B receiving reformulated nonacog alfa for prophylaxis or on-demand treatment were followed up on usual care schedule.

RESULTS: A total of 58 subjects were enrolled, of whom 29 (50%) were less than 18 years of age. Hemophilia was severe (baseline F IX activity < 1%) in 47 (81%) patients. All subjects except one were already treated with reformulated nonacog alfa before enrollment. One subject was receiving reformulated nonacog alfa as immune tolerance induction at time of enrollment. At enrollment, treatment regimen was mainly prophylactic in subjects less than 18 years and on-demand in subjects 18 years or older. Median duration of follow-up in the survey was 3.3 (2.3-3.8) years. The median annualized bleeding rate was 3.9 (1.5-5.2) for prophylaxis regimen and 12.2 (3.9-22.1) for on-demand regimen. One subject, a previously untreated patient, developed F IX inhibitors during follow-up. No allergic reaction, no blood cell agglutination, no lack of efficacy or recovery, and no thrombotic events were reported.

CONCLUSION: Reformulated nonacog alfa was shown to be safe in a usual care setting.

Just like hemophilia A, prevention and treatment of bleeding episodes in hemophilia B, respectively, rely on prophylactic and on-demand regimens, whether plasma-derived or recombinant Factor IX (F IX) products are used to replace deficient F IX.¹

A reformulation of nonacog alfa, a recombinant concentrate of human F IX, was developed to minimize the risk of red blood cell (RBC) agglutination into the tubing or syringe that could have been observed with the original nonacog alfa.² The reformulated nonacog alfa was approved for use in the United States and in the European Union in 2007.

Clinical studies have demonstrated the efficacy and safety of nonacog alfa for on-demand treatment and prophylaxis. While the randomized nature of the clinical studies ensures its high internal validity by removing bias,

ABBREVIATIONS: ABR = annualized bleeding rate; ED(s) = exposure day(s).

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their “controlled” nature requires to be completed by real-world population observations.³ Also, postmarketing investigations are recommended to ensure consistency in the long term between the outcome from preauthorization clinical studies and from routine use.⁴ The following postmarketing noninterventional study was therefore conducted to evaluate the safety and efficacy of reformulated nonacog alfa in a usual care setting in France.

MATERIALS AND METHODS

This is a postmarketing, open-label, multicentric, prospective, observational, and uncontrolled study, conducted in 19 French hemophilia treatment centers, involved in the Réseau FranceCoag. The study is registered on ClinicalTrials.gov under the number NCT00835068. Subjects with hemophilia B already receiving or starting treatment with reformulated nonacog alfa and having dated and signed the informed consent form were enrolled. Exclusion criteria were ongoing treatment of hemophilia B with another F IX concentrate or participation in the European prospective registry of patients with hemophilia B treated with nonacog alfa that collected data from patients treated with original and/or reformulated nonacog alfa.⁵ The primary objective was to collect safety data on reformulated nonacog alfa used under routine clinical practice conditions in France. The secondary objectives were to collect real-life data on the clinical course of patients treated with reformulated nonacog alfa. Subjects followed their usual visit schedule as determined by their physician.

Baseline data collected for all patients included demographics, medical history, date of diagnosis, disease severity, individual and family hemophilia history, F IX inhibitor history, F IX molecular defect if known, known allergies, and a list of F IX concentrate and other F IX-containing blood products received during the year preceding enrollment in the study. Baseline F IX (F IX:C) activity level and Bethesda assay for F IX inhibitor, when available from patient records, were recorded during the follow-up.

All adverse events with a possible causal relationship with reformulated nonacog alfa, particularly those of interest (F IX inhibitor, allergic reaction, RBC agglutination, lack of efficacy, low recovery, thrombotic event), were recorded. During the conduct of the study (6 months before the end of the inclusion period), the sponsor amended the protocol to record all adverse events whatever the relationship with reformulated nonacog alfa. The efficacy was evaluated based on the number of bleeding episodes, the number of infusions of the product, and the dose needed to treat a bleeding episode and F IX consumption.

Prescription treatment regimen was recorded at each visit. The type of prophylaxis regimen recorded was that of the physician prescription.

In addition, preventive administrations (numbers and administered dose), cause of preventive administration (e.g., before a high-risk activity), and adverse events were recorded during each visit and reported in the paper case report form from the patient's diary used in the management of hemophilia and from data collected at the visit.

Safety analysis was performed on all enrolled subjects receiving at least one dose of reformulated nonacog alfa after inclusion. Efficacy analysis was performed on all patients with basal F IX activity of not more than 1%, with a well-documented diary (number of real exposure days [EDs]) which reported equally at least 70% of the planned EDs for each prophylaxis period and without F IX inhibitor (threshold inhibitor titer, 0.6 Bethesda units [BU]) before or during the study.

As the number and frequency of visits depend on several factors including center habits, duration of follow-up in the study, or other patient characteristics, several end-points were estimated on an annual basis (e.g., number of bleeding episodes, number of EDs): a mean annual rate was defined for each patient according to its duration of follow-up in the study. The end of study was planned one year after inclusion of the last patient in the study and with maximum 5 years of follow-up for a given subject.

No formal calculation of sample size was performed because the number of patients who could be included was too low to expect a high study power. Indeed, only patients with a hemophilia diary were included in the study and this reason has decreased the potential of patients expected. To obtain a patient population as representative as possible, the study was to be proposed to all subjects of each center using reformulated nonacog alfa. Neutralizing antibodies and allergic reactions are the most severe adverse events likely to be observed during treatment with F IX. As the incidence of these adverse events is 2% to 3%, data recording over a long period on a sample of 60 to 80 subjects should allow the detection of such cases.^{4,6} Planned enrollment was approximately 60-80 subjects over 4 years.

The statistical analysis is descriptive and was performed using computer software (SAS, Version 9.1.2, SAS Institute). When displayed, ranges are interquartile ranges.

RESULTS

Subjects

Between January 2009 and November 2012, a total of 58 subjects were included by 17 of the 19 centers. All subjects who received at least one dose of nonacog alfa were included in the safety population and 42 (72.4%) subjects were included in the efficacy population. Reasons for exclusion from the efficacy population were as follows: baseline F IX of more than 1% (eight subjects), F IX inhibitor at inclusion (one subject), F IX inhibitor development

TABLE 1. Subject demographics and characteristics at enrollment*

Characteristics	Safety population			Efficacy population		
	<18 years (n = 29)	≥18 years (n = 29)	Total (n = 58)	<18 years (n = 22)	≥18 years (n = 20)	Total (n = 42)
Age (years)	9.6 ± 5.0	36.4 ± 12.1	23.0 ± 16.4	9.7 ± 4.9	36.8 ± 11.8	22.6 ± 16.3
Weight (kg)	28.7 (19.6-47.0)	71.4 (63.0-82.0)	59.2 (28.7-73.0)	29.8 (19.6-50.0)	73.5 (64.0-82.5)	59.2 (28.5-73.0)
F IX:C activity						
<1%	22 (75.9)	25 (86.2)	47 (81.0)	19 (86.4)	20 (100.0)	39 (92.9)
[1-5%]	5 (17.2)	2 (6.9)	7 (12.1)	3 (13.6)	0 (0.0)	3 (7.1)
≥5%	2 (6.9)	2 (6.9)	4 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
HIV infection	0 (0.0)	9 (31.0)	9 (15.5)	0 (0.0)	6 (30.0)	6 (14.3)
Hepatitis C infection	0 (0.0)	19 (65.5)	19 (32.8)	0 (0.0)	14 (70.0)	14 (33.3)
Hepatitis B infection	0 (0.0)	2 (6.9)	2 (3.4)	0 (0.0)	2 (10.0)	2 (4.8)
Prior F IX treatment	28 (96.6)	29 (100)	57 (98.3)	22 (100)	20 (100)	42 (100)
Cumulative EDs, patients with prior F IX						
1-20	4 (14.3)	0 (0.0)	4 (7.0)	2 (9.1)	0 (0.0)	2 (4.8)
21-50	3 (10.7)	1 (3.4)	4 (7.0)	2 (9.1)	0 (0.0)	2 (4.8)
51-100	0 (0.0)	2 (6.9)	2 (3.5)	0 (0.0)	1 (5.0)	1 (2.4)
> 100	21 (75.0)	26 (89.7)	47 (82.5)	18 (81.8)	19 (95.0)	37 (88.1)
Treatment regimen†						
Prophylaxis	21 (72.4)	8 (27.6)	29 (50.0)	19 (86.4)	3 (15.0)	22 (52.4)
On demand	7 (24.1)	21 (72.4)	28 (48.3)	3 (13.6)	17 (85.0)	20 (47.6)

* Data are reported as mean (±SD), median (range), or number (%).

† Treatment regimen at the enrollment visit.

during the study (one subject), no follow-up visit (one subject), and no available diary (five subjects).

All subjects were males, 29 (50.0%) were less than 18 years of age. A family history of hemophilia B was reported in 36 (62.1%) subjects and a family history of F IX inhibitor in one (1.7%) subject (Table 1). A 15.9-year-old subject had been receiving immune tolerance induction for 2 years upon enrollment in the survey because of a F IX inhibitor with a maximum titer level of 11 BU. Once immune tolerance was achieved, data after start of prophylactic therapy were included in the efficacy analysis for that subject.

At the enrollment visit, reformulated nonacog alfa was mainly prescribed as prophylactic treatment in subjects less than 18 years and as on-demand treatment in subjects 18 years and older. The number of patients receiving prophylaxis regimen were, respectively, nine (31.0%) once weekly, 15 (51.7%) twice weekly, and five (17.3%) more than twice weekly.

Safety

The median study follow-up duration of the safety population (58 patients) was 3.3 (2.3-3.8) years with a median of 138 (23-278) EDs corresponding to a total of 8736 EDs. The total consumption of reformulated nonacog alfa throughout the study was 22 million IU. A total of 55 adverse events were reported in 27 subjects, including 12 serious adverse events in 11 subjects (Table 2) and five drug-related adverse events (physician's judgment) in two patients (Table 3). One subject developed F IX inhibitor: a 23-month previously untreated patient with severe

TABLE 2. List of serious adverse events reported during the study*

System organ class/preferred term	Subjects n = 58
Blood and lymphatic system disorders	1 (1.7)
F IX inhibition	1 (1.7)
Musculoskeletal and connective tissue disorders	4 (6.9)
Back pain	1 (1.7)
Hemarthrosis	1 (1.7)
Hemophilic arthropathy	1 (1.7)
Muscle hemorrhage	1 (1.7)
General disorders and administration site conditions	3 (5.2)
Device failure†	1 (1.7)
Hyperthermia	1 (1.7)
Pyrexia	1 (1.7)
Ear and labyrinth disorders	2 (3.4)
Otitis media	1 (1.7)
Tympanic membrane perforation	1 (1.7)
Congenital, familial, and genetic disorders	1 (1.7)
Congenital genitourinary abnormality	1 (1.7)
Infections and infestations	1 (1.7)
Appendicitis	1 (1.7)

* Data are reported as number (%).

† The device failure corresponded to the unsealing of a shoulder prosthesis.

hemophilia B and a large F IX gene deletion. The inhibitor occurred at 12 exposure days. No allergic reaction, no blood cell agglutination, no lack of efficacy or recovery, and no thrombotic events were reported in the safety population.

Efficacy

A total of 53 (91.4%) subjects of the safety population and the 42 subjects of the efficacy population were followed

TABLE 3. Adverse drug reactions

Age (years)*	Preferred term	System organ class	Months from enrollment	ADR duration (days)	Serious AE	Intensity	Action(s) taken
31.5	Dizziness	Nervous system disorders	26.1	1	No	Mild	None
	Dizziness	Nervous system disorders	26.1	1	No	Mild	None
	Dizziness	Nervous system disorders	26.2	1	No	Mild	None
	Headache	Nervous system disorders	37.8	38	No	Mild	New batch
1.3	F IX inhibition	Blood and lymphatic system disorders	7.4	160	Yes	Severe	Discontinuation†

* Age upon enrollment.

† Nonacog alfa was discontinued and the subject withdrawn from the study.

ADR = adverse drug reaction; AE = adverse event.

1 year or more in the study. The median duration of follow-up of the efficacy population (42 patients) was 3.4 (2.6-3.9) years.

Eleven patients (19.0%) prematurely discontinued the study, most of the time (seven of 11) due to the investigator's decision to include the patient in another clinical study. The other reasons for premature withdrawal were as follows: adverse events for one patient (F IX inhibitor) possibly related to reformulated nonacog alfa; the death of one patient which occurred during the study (316 days after inclusion) and was regarded as not related to nonacog alfa; and the investigator's decision to switch two patients to another F IX treatment.

Of these 42 subjects included in the efficacy population, 28 (66.7%) subjects experienced at least one period of prophylaxis regimen and 21 (50.0%) subjects experienced at least one period of on-demand regimen. Median duration of prophylaxis regimen was 1064 (365-1270) days. Median duration of on-demand regimen was 1072 (652-1296) days. During follow-up, 19 (45.2%) subjects received at least one preventive injection of nonacog alfa. Median consumption of nonacog alfa was 44.3 (36.7-51.7) IU/kg per injection for prophylaxis regimens and 48.1 (38.6-55.9) IU/kg per injection for on-demand regimen.

All but four (who were on prophylaxis regimen) subjects experienced at least one bleeding episode during the follow-up. The median annualized bleeding rate (ABR) was 3.9 (1.5-5.2) during prophylaxis treatment periods and 12.2 (3.9-22.1) during on-demand treatment periods. Most of the bleeding episodes associated with an on-demand regimen were hemarthrosis while hematomas, hemarthrosis, and other bleeding were equally observed when on prophylaxis (Fig. 1). More than one injection of nonacog alfa was needed to treat the bleeding episode in 117 (44.8%) and 179 (25.8%) of the bleeding episodes under prophylaxis and on-demand regimen, respectively.

DISCUSSION

The objective of this noninterventional study was to evaluate the overall safety and efficacy of reformulated nonacog alfa in a usual care setting in France. The total

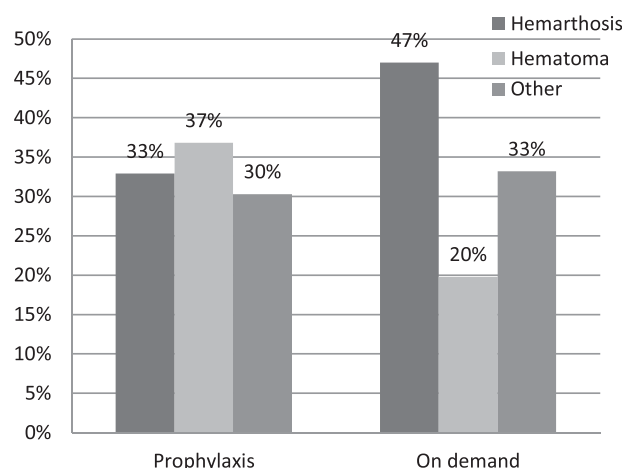


Fig. 1. Type of bleeding episodes according to type of replacement of clotting factor. A total of 261 and 695 episodes of bleeding were reported under prophylaxis and on-demand regimen, respectively.

cumulative number of EDs of the present survey was 8736 and the total consumption of reformulated nonacog alfa was 22 million IU. Overall, the incidence of adverse events and of serious adverse events was low. Only one subject was discontinued from the study due to F IX inhibitor development (a previously untreated patient with a large F IX gene deletion) and one death unrelated to nonacog alfa was reported. Previously, one publication has reported events of RBC agglutination (the visual observation of RBC clumping in tubing or syringe during intravenous recombinant F IX administration) for two of 63 patients receiving the original nonacog alfa formulation.⁷ These events were resolved without any clinical sequel. No other cases have been reported either with the original formulation or with the reformulated formulation that has been developed to minimize the risk of RBC agglutination.

In this study, 19% of the patients prematurely discontinued the investigation, mostly due to their inclusion in another clinical trial (seven patients on 11). For the four remaining patients, the investigator decided for two of them to use another F IX, one patient died of digestive

hemorrhage, not related to reformulated nonacog alfa, and one patient experienced an adverse event (F IX inhibitor) possibly related to reformulated nonacog alfa and therefore decided to stop the present investigation. Nevertheless, this rate is neither high nor surprising in this type of study and for this kind of pathology. Indeed, a previous open-label, noninterventional, prospective, and observational cohort study conducted by Berntorp and colleagues,⁵ on 218 patients with hemophilia B, had a discontinuation rate of 52%, primarily due to the lack of interest of the patients in continuing the study. We also noticed that, as the reported incidence of F IX inhibitor was 2% to 3%, it has been estimated that data recording over a long period on a sample of 60 to 80 patients should allow the detection of such cases, even though no calculation of sample size was performed for this study.^{4,6}

In this study, no event of special interest including allergic reaction, lack of efficacy, or recovery thrombosis or RBC agglutination, except one patient with F IX inhibitor, was observed. No new safety signals were noted during the survey period. The study data reported herein for reformulated nonacog alfa supports the safety of nonacog alfa as reported in previous clinical trials in adults and children⁸⁻¹⁰ in a retrospective safety analysis¹¹ and in a European registry.⁵

The doses per infusion reported in this study are within the ranges of clinical trials with F IX.¹² Moreover, the mean doses of F IX in IU/kg per injection were approximately the same for the on-demand and prophylaxis regimens: 49 ± 14 and 45 ± 11 IU/kg, respectively. It should be noted that these kind of data were also observed in a recent cost-effectiveness study EQOFIX, also conducted on patients from centers included in the Réseau FranceCoag. We can suppose that similar trends in the mean doses per injection of F IX between the two regimens are likely related to the standards of care applied in these centers.¹³ Otherwise, only 31% of patients were on once-weekly prophylaxis with not a higher dosage than in the twice-weekly regimen. These real-world data reflect the practice in France. Also, at some point in the study, 19 patients (44%) received a preventive regimen for a mean period of 35 days, only for exceptional situations as an intense activity (sport) or a surgery. Considering that the study had a mean duration of 1235 days, these data are not relevant for this analysis.

This study confirms that ABR is much lower with prophylaxis regimen compared to an on-demand regimen. However, the ABR for patients with on-demand regimen was lower in the present study than in a study previously published by Valentino.¹⁰ This is likely due to a selection of patients with a higher bleeding tendency in the study published by Valentino (for which inclusion criteria was 12 bleeds within the past 12 months). In the prophylaxis group, the ABR is not so different than that in other studies.

The number of infusions necessary to treat a bleed was reported to be higher when a prophylaxis regimen was used. As this is unusual, we can hypothesize that patients who are on on-demand treatment are less keen to have repeated infusion for a bleed although patients on prophylaxis are more compliant to have a second infusion for bleeding, which is part of French recommendations. In conclusion, the present real-world study confirms the safety and efficacy of reformulated nonacog alfa.

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CONFLICT OF INTEREST

TL received consulting fees and/or reimbursement for attending symposium from Baxter, Bayer, Biogen, Ipsen, LFB, Novo Nordisk, Octapharma, Pfizer, and Roche; CR received grants from Novo Nordisk and CSL Behring and personal fees from Baxter, CSL Behring, LFB, Novo Nordisk, and Sobi and participates in clinical trials for all these companies; MT received speaking fees and funding for research from Pfizer; and SA is a Pfizer employee. All other authors has disclosed no conflicts of interest.

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