Application Type	Original BLA
STN	125611/0
CBER Received Date	June 3, 2016
PDUFA Goal Date	June 3, 2017
Division / Office	DB/OBE
Committee Chair	Chava Kimchi-Sarfaty, PhD
Clinical Reviewer(s)	Megha Kaushal, MD, MSHS
Project Manager	Edward Thompson
Priority Review	No
Reviewer Name(s)	Renée Rees, PhD for Judy Li, PhD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée Rees, PhD, Team Leader, Therapeutics Evaluation Branch Boguang Zhen, PhD, Chief, Therapeutics Evaluation Branch John Scott, PhD, Acting Division Director, Division of Biostatistics
Applicant	Novo Nordisk
Established Name	Nonacog beta pegol
Dosing Regimen	For intravenous infusion after reconstitution only
Indication(s) and Intended Population(s)	On demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia B.

Table of Contents

GLOSSARY

AE   Adverse Event
ABR   Annualized Bleeding Rate
BLA   Biologics License Application
BU   Bethesda Unit
EDs   Exposure Days
EMA   European Medicines Agency
FIX   Coagulation Factor IX
GCP   Good Clinical Practice
HCP   Host Cell Proteins
ICH   International Conference on Harmonisation
LAR   Legally Acceptable Representative
LOCF   Last Observation Carried Forward
MESI   Medical Event of Special Interest
PEG   Polyethylene Glycol
PK   Pharmacokinetics
PUPs   Previous Treated Patient
SAE   Serious Adverse Event
WFH   World Federation of Hemophilia

1. EXECUTIVE SUMMARY

The applicant submitted a biologics license application (BLA) for Coagulation Factor IX (recombinant), pegylated, also referred to as nonacog beta pegol, for the proposed indication of on demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia B. The submission includes data from four completed studies (pivotal, pediatric, surgery and extension) on previously treated subjects.

In the pivotal study (study 3747), the hemostatic response rate for the treatment and control of bleeding episodes for subjects in both the prophylaxis treatment and on-demand treatment groups is 92.2% (95% CI: 86.9; 95.4), which meets the pre-established success criteria of a lower confidence bound above 65%. The estimated mean annualized bleeding rate (ABR) for 40 U/kg once weekly prophylaxis subjects is 2.51 (95% CI: 1.42; 4.43), which also meets the success criteria of an upper confidence bound below 4.8.

In the pediatric study (study 3774), the estimated mean ABR was 1.44 (95% CI: 0.92, 2.26) and the hemostatic efficacy overall success rate was 92.9%.

The hemostatic efficacy of nonacog beta pegol success rate was 100% in the surgery study (study 3773).

None of the subjects in the four studies developed inhibitory antibodies, and the one death was evaluated as unlikely related to nonacog beta pegol. There were no statistical issues identified during the review of this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B is an X-linked recessive congenital bleeding disorder, caused by mutations in the coagulation factor IX (FIX) gene, with an incidence of approximately one in every 30,000 male births. There are two main modes of therapy for hemophilia B subjects: preventive treatment (prophylaxis) and episodic treatment (on-demand).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The BLA was developed under IND 14008. A Type B meeting was held on October 25, 2010, to discuss the study design of the pivotal study and the statistical analysis plan. FDA requested the applicant to provide clarification on the analysis model and study success criteria for the pivotal study.

On March 18, 2013, nonacog beta pegol was granted orphan drug designation for routine prophylactic administration for prevention of bleeding in subjects with hemophilia B (designation request #09-2765).

A pre-BLA meeting was scheduled for April 28, 2015. FDA sent the applicant a written response on April 22, 2015, addressing the applicant's questions regarding the planned application; no statistical issues were raised in the meeting request.

Subsequent to the BLA filing, an Information Request (IR) for analysis program codes was made for verification of study results. The applicant provided the information in Amendment #20 of the BLA application.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Of the six studies in the clinical development program, this review focuses on the pivotal study (study 3747), pediatric study (study 3774), surgery study (study 3773), and extension study (study 3775).

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review memo was based on draft labeling (module 1.14.1); the protocol and its amendment (module 5.3.5.2), study report body (module 5.3.5.2), the data files (module 5.3.5.2) for each of the four studies; and reports from analysis of data from more than one study (module 5.3.5.3) submitted in STN 125611/0. The SAS program codes submitted in STN 125611/0/20 were also reviewed.

5.3 Table of Studies/Clinical Trials

Table 1. Summary of clinical studies

Type of Study	Trial ID,	Trial and Objectives	Subjects Exposed	Test product(s), Dosage regimen, Route of Administration	Trial Design and Type of Control	Duration of treatment	Study Status, Type of Report, Report (CTR) location
Previously treated patients with haemophilia B							
Pharmacokinetic	NN7999-3639	To determine the safety of ascending single intravenous doses of 40K glycopegylated recombinant factor IX (nonacog beta pegol) in patients with haemophilia B (factor IX≤2%) at three dose. Comparing pharmacokinetics of nonacog beta pegol and patients previous product	Total: 16 adult patients (21-55 years) with haemophilia B PK: 15 patients	25 IU/kg, 50 IU/kg and 100 IU/kg. i.v.	*First human dose trial* A Multi-Centre, Multi-National, Open-Label, Dose Escalation Trial Evaluating Safety and Pharmacokinetics of Ascending Intravenous Doses of 40K Pegylated Recombinant FIX in Non-Bleeding Patients with Haemophilia B.	Single dose	Completed; Full Module 5.3.3.2, NN7999-3639
Safety and Efficacy	NN7999-3747	To evaluate pharmacokinetics, safety and efficacy of nonacog beta pegol in prevention and treatment of bleeding episodes.	Total: 74 adolescent or adult patients (13-65 years) with haemophilia B Prophylaxis: 59 patients On-demand:15 patients PK (3 batches): 16 patients	*Prophylaxis:* 10 IU/kg or 40 IU/kg once weekly. *Treatment of bleeding episodes:* 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes). *Pharmacokinetics:* 10 or 40 IU/kg single dose and steady-state. i.v.	*Pivotal trial* A multicentre, single-blind, non-controlled, randomised trial evaluating safety, efficacy and pharmacokinetics of nonacog beta pegol when used for routine prophylaxis and treatment of bleeding episodes in patients with haemophilia B.	Multiple dose	Completed; Full Module 5.3.5.2, NN7999-3747
Safety and Efficacy	NN7999-3773	To evaluate safety and efficacy of nonacog beta pegol throughout the surgical period	Total: 13 adolescent or adult patients (15-56 years) with haemophilia B	*Pre-operative loading dose:* 80 IU/kg *Post-operative dose(s):* 40 IU/kg	*Surgery trial* A multicentre, open-label, non-controlled trial evaluating efficacy and safety of nonacog beta pegol during major surgical procedures in patients with haemophilia B.	Multiple dose	Completed; Full Module 5.3.5.2 NN7999-3773
Safety and Efficacy	NN7999-3774	To evaluate pharmacokinetics, safety and efficacy of nonacog beta pegol in paediatric patients.	Total: 25 paediatric patients (1-12 years) with haemophilia B. PK: 25 patients. 22 patients continued into the extension phase of the trial.	*Prophylaxis:* 40 IU/kg once weekly. *Treatment of bleeding episodes:* 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes). i.v.	*Paediatric trial* A multicentre, open-label, non-controlled trial evaluating safety, efficacy and pharmacokinetics of nonacog beta pegol when used for routine prophylaxis and treatment of breakthrough bleeding episodes in children with haemophilia B.	Multiple dose	Main phase completed; Full Module 5.3.5.2 NN7999-3774 Extension phase ongoing
Safety and Efficacy	NN7999-3775	To evaluate, safety, efficacy, patient reported outcomes and health economic impact of nonacog beta pegol.	Total: 71 adolescent or adult patients (14-66 years) with haemophilia B	*Prophylaxis:* 10 IU/kg or 40 IU/kg once weekly. *Treatment of bleeding episodes:* 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes).	*Extension trial* A multicentre, open label, non-controlled trial evaluating long-term safety and efficacy of nonacog beta pegol when used for routine prophylaxis and treatment of bleeding episodes in patients with haemophilia B. Patients enrolled in the trial could be recruited from the pivotal trial (Trial 3747) or the surgery trial (Trial 3773).	Multiple dose	Completed; Full Module 5.3.5.2 NN7999-3775
Previously untreated patients with haemophilia B							
Safety and Efficacy	NN7999-3895	To evaluate pharmacokinetics, safety and efficacy of nonacog beta pegol in previously untreated patients..	The planned number of patients to be exposed is 50.	*Prophylaxis:* 40 IU/kg once weekly. *Treatment of bleeding episodes:* 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes).	*Trial in previously untreated patients* This is a multicentre, open label, single-arm, non-controlled trial evaluating safety and efficacy of nonacog beta pegol in prophylaxis and treatment of breakthrough bleeding episodes in previously untreated patients with haemophilia B.	Multiple dose	Ongoing

Source: BLA 125611/0, Module 5.2, Tabular listing of all clinical studies, page 2-5

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

NN7999-3747 (Pivotal Study)

6.1.1   Objectives (Primary, Secondary, etc.)

Primary objective: To evaluate the immunogenicity of nonacog beta pegol.

Secondary objectives included the evaluation of:
- clinical efficacy of hemostasis (treatment of bleeding episodes)
- clinical efficacy in long term bleeding prophylaxis (number of bleeding episodes during prophylaxis)
- the efficacy by the surrogate marker for efficacy, FIX activity
- general safety of nonacog beta pegol

6.1.2 Design Overview

This was a multinational, multi-center trial consisting of two prophylaxis arms (low dose and high dose) and one on-demand arm. Whether a subject would be in a prophylaxis arm or in the on-demand arm was the choice of the subject and investigator, and was decided at the screening visit (Visit 1). Randomization to one of the two prophylaxis arms was done at Visit 2. Each subject in a prophylaxis arm was to attain 50 exposure days (EDs) to nonacog beta pegol throughout the trial. Subjects on prophylaxis did not know which dose they were randomized to. This information was also concealed from the investigator. However, as the investigator had the possibility to measure FIX activity levels during the trial, the investigator could potentially be unblinded during the trial. In substantial amendment # 2, it was added to the protocol that subjects in the United States were only to be assigned to the on-demand arm of this trial until 20 bleeds in a minimum of 10 subjects were treated.

Reviewer Comment: This is not a randomized clinical trial for purposes of comparing prophylaxis and on-demand treatment.

6.1.3 Population

The following inclusion criteria were applied:
- male
- age 13-70 years (both inclusive) (except for the Netherlands where the lower age limit was 18 years),
- Body Mass Index is <35,
- moderately severe or severe congenital hemophilia B with a FIX activity ≤ 2% according to medical records;
- a history of at least 150 EDs to other FIX products;
- Currently treated on-demand with at least 6 bleeding episodes during the last 12 months or at least 3 bleeding episodes during the last 6 months, or currently on prophylaxis.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects enrolled in a prophylaxis arm received either 10 U/kg (low dose arm) or 40 U/kg (high dose arm) nonacog beta pegol doses once weekly (every 7th day ± 24 hours), depending on which prophylaxis arm they were randomized to.

Subjects in the on-demand arm received doses of 40 U/kg or 80U/kg depending on the bleed.

6.1.6 Sites and Centers

Subjects were screened at 40 sites, and were enrolled at 39 sites. The 39 sites span 13 countries: France (1), Germany (3), Italy (2), Japan (5), Macedonia (2), Malaysia (1), Netherlands (1), Russia (2), South Africa (1), Thailand (2), Turkey (3), United Kingdom (4), and the United States (12).

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint: Incidence of inhibitory antibodies against FIX defined as titer ≥0.6 Bethesda Unit (BU).

For the calculation of the inhibitor rate, the numerator included all subjects with inhibitory antibodies, while the denominator included all subjects with a minimum of 10 EDs plus any subjects with less than 10 EDs but with inhibitory antibodies. Adequate safety with regard to inhibitory antibodies would be concluded if the observed rate was lower than or equal to 2%, which is equivalent to zero or one inhibitors occurring and yields an upper one-sided 97.5% confidence limit below or equal to 10.7%.

Reviewer Comment: Per my discussion with the clinical reviewer, inhibitors usually form in previously treated subjects (PTPs) within the first 10-15 EDs. The reason subjects with less than 10 EDs were excluded from the denominator may be because those subjects haven't been exposed long enough to have an inhibitor response yet. Although I don't believe it is necessary to exclude those subjects from the denominator when calculating the inhibitor incidence it is acceptable approach since it generates a more conservative inhibitor incidence rate of the test product.

Key Secondary Efficacy Endpoints
- Hemostatic effect for treatment of bleeding episodes, assessed as success/failure based on a four-point scale for hemostatic response (excellent, good, moderate and poor) by counting excellent and good as success and moderate and poor as failure. The four-point scale was defined as below and took into account the improvement in signs of bleeding, mainly by pain relief, but also took swelling and motion into account. The evaluation was made by the made by the subject or Legal Acceptable Representative (LAR) to reflect the hemostatic response from the time of treatment and until eight hours after the treatment had been administered:
    - Excellent: abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single injection

- Good: noticeable pain relief and/or improvement in signs of bleeding within hours after a single injection
- Moderate: probable or slight beneficial effect within the first 8 hours after the first injection but requiring more than one injection within 8 hours
- Poor: no improvement,

The success criterion is that the success rate is not lower than 65%.

- Number of bleeding episodes per subject during routine prophylaxis

The success criterion is that both the highest dose and the lowest dose, individually, have a bleeding frequency less than 4.8 bleeding episodes per year. This is tested by evaluating whether the upper confidence limit for the ABR is below 4.8.

Additional Supportive Efficacy Endpoints
- FIX trough levels
- Number of bleeding episodes per subject during routine prophylaxis by type of bleed
- Number of injections of nonacog beta pegol required per bleeding episode
- Amount of nonacog beta pegol required per bleeding episode (U/kg BW/bleeding episode)

Safety Endpoints
- Adverse events and serious adverse events
- Host Cell Proteins (HCP)-antibodies
- General safety endpoints including laboratory parameters, physical examination and vital signs

6.1.9 Statistical Considerations & Statistical Analysis Plan
Sample size
The primary objective of the trial is to evaluate the immunogenicity of nonacog beta pegol. Given the rarity of the disease, a sample size of 50 subjects treated for approximately 50 EDs was chosen to allow for a reasonable evaluation of inhibitor formation in this pivotal trial. Subjects treated on-demand will provide additional EDs to nonacog beta pegol.

Analysis Sets
The full analysis set and the safety analysis set both consisted of all subjects exposed to nonacog beta pegol. The full analysis set was used for all efficacy analyses. Safety analyses were performed on the safety analysis set, with the exception of the primary endpoint analysis (see my Reviewer Comment in Section 6.1.8).

Statistical Methods
The statistical testing was performed in a hierarchical format.

Primary Endpoint
The rate of inhibitory antibodies was reported and a one-sided 97.5% upper confidence limit was provided using the Clopper-Pearson exact binomial method.

Key Secondary Efficacy Endpoints
1. Hemostatic response to treatment of acute bleeding episodes was to be tested if and only if the analysis of the primary endpoint is successful. Logistic regression was used to calculate the lower 95% confidence limit for the success rate (see Reviewer Comment in Section 6.1.11.2).

2. Number of bleeding episodes per subject during routine prophylaxis would only be analyzed if the analysis of the primary endpoint (inhibitor rate) and the first secondary endpoint (hemostatic response) are successful. The endpoint was analyzed by a Poisson regression model with dose as a factor, further allowing for over-dispersion and using treatment duration as an offset. ABR estimates for each dose were provided along with 95% CIs.

   The test of the ABR will also be performed in a hierarchical format according to dose. The first test will aim to establish that the 40U/kg dose meets the success criterion based on the Poisson regression model. If the 40U/kg group is demonstrated to meet this criterion, a similar evaluation will be performed for the 10 U/kg dose.

   In addition, based on the Poisson regression, the 10U/kg dose will be compared statistically to the 40 U/kg dose by a test of the null hypothesis of no difference between doses.

Missing Data
All analyses were based on all available information until the last visit. If not otherwise specified, withdrawn subjects contributed data until the date of withdrawal. Treatment duration was included as an offset covariate in the Poisson regression model for routine prophylaxis, which incorporates subjects who withdrew prior to 52 weeks of treatment.

A sensitivity analysis for prophylaxis treatment was also conducted using the last observation carried forward (LOCF) approach for all withdrawn subjects who have at least 1 month prophylaxis treatment duration. The imputation was not conducted for those subjects who withdrew within 1 month due to the short exposure time and the uncertainty of the LOCF values. A sensitivity analysis for hemostatic effect was added (i.e., not pre-specified) where bleeding episodes with a missing response evaluation were treated as failures.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
Both the full analysis set and safety analysis set contain 74 subjects.

6.1.10.1.1 Demographics
The trial population consisted of males with a median age of 30 years (ranging from 13 to 65 years old). Of the 74 exposed subjects, 18 subjects were adolescents (13-17 years). The median weight of all subjects was 72.6 kg (ranging from 36.0 to 108.1 kg). The majority of the subjects were White (64.9%); the second largest group was Asian (21.6%). A total of 28% of the subjects were from the US, 12% from the United Kingdom, 11% from Japan, while the remaining subjects were distributed between the other 10 countries listed in Section 6.1.6

6.1.10.1.3 Subject Disposition
A total of 86 subjects were screened for this trial (Figure 1) and 74 subjects were enrolled.

Figure 1. Subject disposition
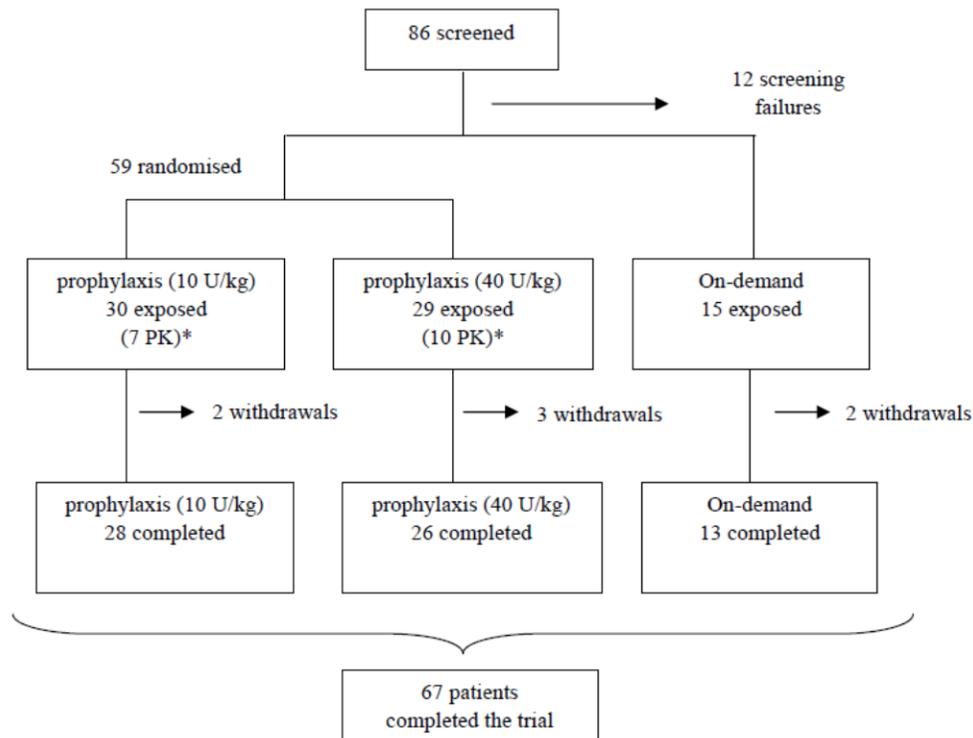
Source: BLA125611/0 Module 5.3.5.2 report-body_study3747.pdf figure 10-1, page 111 of 1237.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

There were no primary efficacy endpoints. Please see Section 6.1.12.5 for the primary safety endpoint.

6.1.11.2 Analyses of Secondary Endpoints

Hemostatic Response

Since the primary safety endpoint success criterion was met (see Section 6.1.12.5), the hemostatic response could be analyzed. Out of the 345 bleeding episodes (in both prophylaxis and on-demand subjects), 341 bleeds were rated, of which 315 bleeds were rated as a success. The model-based hemostatic success rate for all bleeds was 92.2% (95% CI: 86.9; 95.4), and the hemostatic effect was confirmed since the lower limit of the 95% CI was above 65%.

For the subjects on the 40 U/kg prophylaxis dose, 67 out of 69 breakthrough bleeds were rated as success; the model-based success rate was 97.1% (95% CI: 90.0, 99.2). The success rate of hemostatic responses for the 40 U/kg arm was numerically higher compared with the 10 U/kg arm. Table 2 lists the hemostatic response for all bleeds and by treatment group.

Reviewer Comment: The analysis for the hemostatic responses included in the original individual study report was based on a logistic regression model assuming independent working correlation (response success rate 92.4% with 95% CI: 87%, 95.6%). However, the protocol stated that a repeated statement should be used which takes correlation within subjects into account. Note that the results yield the same analysis result since both lower limits of the CI (87% and 86.9%, respectively) meet the success criterion. The applicant conducted an additional analysis assuming exchangeable correlation within subjects after finalization of the clinical trial report, and reported the result in the summary-clin-efficacy-fix-deficiency.pef (module 5.3.5.2).

Table 2. Hemostatic response by treatment group (full analysis set)

| | Prophylaxis | | | | |
	10 U/kg	40 U/kg	Both	On-Demand	Total
Number of patients	30	29	59	15	74
Number of patients with bleeds, N (%)	25 (83.3)	16 (55.2)	41 (69.5)	14 (93.3)	55 (74.3)
Number of bleeds	132	70	202	143	345
Haemostatic response, N (%)					
N	132 (100.0)	70 (100.0)	202 (100.0)	143 (100.0)	345 (100.0)
Excellent	41 (31.1)	35 (50.0)	76 (37.6)	43 (30.1)	119 (34.5)
Good	72 (54.5)	32 (45.7)	104 (51.5)	92 (64.3)	196 (56.8)
Moderate	13 (9.8)	2 (2.9)	15 (7.4)	7 (4.9)	22 (6.4)
Poor	4 (3.0)	0 (0.0)	4 (2.0)	0 (0.0)	4 (1.2)
Missing	2 (1.5)	1 (1.4)	3 (1.5)	1 (0.7)	4 (1.2)
Success/failure					
N	130 (100.0)	69 (100.0)	199 (100.0)	142 (100.0)	341 (100.0)
Success	113 (86.9)	67 (97.1)	180 (90.5)	135 (95.1)	315 (92.4)
Failure	17 (13.1)	2 (2.9)	19 (9.5)	7 (4.9)	26 (7.6)
Success rate					
Rate	86.9	97.1	90.5	95.1	92.4
95% CI	76.5 ; 93.1	90.0 ; 99.2	82.8 ; 94.9	87.0 ; 98.2	87.0 ; 95.6
P-value*	<0.001	<0.001	<0.001	<0.001	<0.001

Analysed using logistic regression accounting for repeated measures within patients assuming independent working correlation.
* P-values are from the 1-sided test of the null hypothesis that the response rate is less than 65% evaluated at the 2.5% level.
Source: BLA 125611/0 Module 5.3.5.2 report-body_study3747.pdf table 11-3 page 127 of 1237

ABR

Since the hemostatic response endpoint success criteria were met, the number of bleeding episodes per subject during routine prophylaxis could be analyzed. Based on the Poisson model, the estimated mean ABR for 40 U/kg once weekly prophylaxis subjects is 2.51 [95% CI: 1.42; 4.43]), Since the success criteria for the number of bleeding episodes per subject for the 40 U/kg dose was met, the same analysis was done for the 10 IU/kg dose group. The estimated mean ABR for 10 IU/kg once weekly prophylaxis subjects was 4.56 [95% CI: 3.01; 6.90]) and it failed the success criteria. No statistically significant difference in the reduction of ABR between the two doses was found. Table 3 lists details of the ABR for each prophylaxis dose group.

Table 3. Annualized bleeding rate (full analysis set)

	Prophylaxis		
	10 U/kg	40 U/kg	Both
Number of patients	30	29	59
Number of patients with bleeds, N (%)	25 (83.3)	16 (55.2)	41 (69.5)
Number of bleeds	132	70	202
Bleeds per patient (min ; max)	0.0 ; 17.0	0.0 ; 17.0	0.0 ; 17.0
Mean treatment period (years)	0.97	0.96	0.96
Individual ABRs			
N	30	29	59
Median	2.93	1.04	2.04
Interquartile range	0.99 ; 6.02	0.00 ; 4.00	0.00 ; 5.00
Poisson estimate of ABR	4.56	2.51	3.55
95% CI	3.01 ; 6.90	1.42 ; 4.43	2.53 ; 4.98
P-value*	0.402	0.013	0.040
Estimated ABR reduction**			
40 U/kg vs. 10 U/kg	–	–	0.45
95% CI	–	–	-0.11 ; 0.73
P-value***	–	–	0.097

Based on a Poisson regression model with dose as a factor allowing for over-dispersion and using treatment duration as an offset.
*P-values are from the 1-sided test of the null hypothesis that the ABR is at least 4.8 evaluated at the 2.5% level.
**Reduction = 1 – ABR relative risk. Positive values indicate a decrease in bleeding rate and negative values indicate an increase.
***2-sided test of the null hypothesis that there is no difference between the two doses evaluated at the 5% level.
Abbreviations: ABR = Annualised bleeding rate

Source: BLA 125611/0 Module 5.3.5.2 report-body_study3747.pdf table 11-5 page 129 of 1237.

6.1.11.3 Subpopulation Analyses

Hemostatic Response

Table 4 details the comparisons of hemostatic responses by race for the subjects on the prophylaxis 40U/kg dose. It can be seen that the success rate of Asian subjects is numerically slightly lower than that of White subjects and African American subjects. Table 5 compares the hemostatic responses for the 40 U/kg subjects by age groups and there is no evidence of major differences. No statistical comparisons were performed between subgroups.

Table 4. Hemostatic response of the 40 U/kg group subjects by race

Race	Number of responses	Number of successes	Success rate
Asian	19	18	94.7%
Black/African American	5	5	100%
White	45	44	97.8%
Other	0	0	0

Source: BLA 125611/0 Module 5.3.5.2 report-body_study3747.pdf 14.2.29 page 238 of 1237

Table 5. Hemostatic response for 40U/kg group subjects by age groups

	Number of responses	Number of successes	Success rate
13-17 years	20	20	100%
18-70 years	49	47	95.9%

Source: BLA 125611/0 Module 5.3.5.2 report-body_study3747.pdf 14.2.21-22 page 223 of 1237

ABR

Tables 6 and 7 include a comparison of the ABR for the subjects on the 40 U/kg prophylaxis dose by race and age, respectively. The ABR for Asian subjects is numerically higher than for African American or White subjects. ABRs were numerically similar for adolescents and adults. No statistical testing was performed for these subgroups.

Table 6. ABR for the 40U/kg group subjects by race

	Asian	Black/African American	White	Other
Number of Subjects	5	3	21	0
Number of Subjects with bleeds	4	2	10	0
Number of bleeds	19	5	46	0
Mean (median)	10.67 (5)	1.66 (1.98)	2.09 (0)	-
Min, Max	0, 37.78	0, 3	0, 15.11	-
Poisson estimate of ABR	4.59	2.14	2.15	-
95% CI	1.35, 15.65	0.98, 4.69	1.04, 4.41	-

Source: BLA 125611/0 Module 5.3.5.2 report-body_study3747.pdf 14.2.40 page 263 of 1237

Table 7. ABR for the 40 U/kg group subjects by age

	13-17 years	18-70 years
Number of Subjects	9	20
Number of Subjects with bleeds	5	11
Number of bleeds	20	50
Mean (median)	2.18 (1.93)	4.13 (1.03)
Min, Max	0, 6.75	0, 37.78
Poisson estimate of ABR	2.18	2.67
95% CI	0.93, 5.10	1.31, 5.44

Source: BLA 125611/0 Module 5.3.5.2 report-body_study3747.pdf 14.2.59 page 295 of 1237

6.1.11.4 Dropouts and/or Discontinuations

There were missing hemostatic response ratings for four bleeding episodes. A sensitivity analysis of hemostatic effect was conducted where missing response ratings were treated as failures. The results support the original analysis.

Two sensitivity analyses were conducted for the ABR. In the first, subject withdrawals with at least 1 month of prophylaxis treatment (two subjects in the 40 U/kg arm and two subjects in the 10 U/kg arm) were included using a LOCF approach. In the second,

withdrawals without any bleeds in the trial were assigned an annual bleeding rate of 12. Both analyses supported the results of the original analysis.

6.1.12 Safety Analyses

6.1.12.3 Deaths
No deaths were reported.

6.1.12.4 Nonfatal Serious Adverse Events
Four of the AEs were serious, which include hip fracture, skin ulcer, retroperitoneal hematoma and abdominal pain. None of them were judged to be related to nonacog beta pegol by the investigator.

6.1.12.5 Adverse Events of Special Interest (AESI)
No unexpected safety issues were identified in the trial. No inhibitory antibodies were detected and the 1-sided 97.5% upper confidence limit for the inhibitory antibody incidence rate of zero was 6%, which meets the safety success criteria.

Anti-nonacog beta pegol binding antibodies were confirmed in three subjects, but none of the anti-nonacog beta binding antibodies detected in the three subjects had any inhibitory effect.

6.2. Trial #2
NN7999-3774 (Pediatric Study)

6.2.1 Objectives (Primary, Secondary, etc.)
Primary objective: To evaluate immunogenicity of nonacog beta pegol in children with hemophilia B.

Secondary objectives included the evaluation of:
- safety other than immunogenicity
- efficacy in long-term prophylaxis and in the treatment of breakthrough bleeding episodes
- efficacy through the surrogate marker for efficacy, FIX activity

6.2.2 Design Overview
This was a multicenter, multinational, open-label, non-controlled, single-arm, confirmatory study evaluating safety, efficacy and pharmacokinetics (PK) of nonacog beta pegol in prophylaxis and on demand treatment of bleeding episodes (hereafter referred to as "treatment of bleeding episodes") in children with hemophilia B. The study was divided into a main phase (core study) of 52 weeks, followed by an optional extension phase.

Subjects received an initial 40 U/kg dose of nonacog beta pegol at the clinic, followed by a PK session. The second dose was administered at the study site after the last PK sample

had been collected, i.e. one week after the first dose. The subsequent doses were then administered once weekly at home or at the study site. At the end of the main phase, subjects that were not continuing in the extension phase were scheduled for a follow-up visit where they were tested for inhibitors.

6.2.3 Population

The study enrolled previously treated children (≤12 years) with hemophilia B and a FIX activity level ≤2%.

Inclusion criteria include the following:
- Informed consent obtained before any study-related activities. (Study-related activities are any procedure that would not have been performed during normal management of the subject.)
- Male subjects with moderately severe or severe congenital hemophilia B with a FIX activity level ≤2% according to medical records.
- Age ≤12 years (until subject turns 13 years, at time of inclusion).
- Body weight ≥10 kg
- History of at least 50 EDs to other FIX products.
- The subject and/or parent(s)/caregiver are capable of assessing a bleeding episode, keeping an eDiary, conducting home treatment and otherwise able to follow trial procedures.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Prophylaxis
All subjects received 40 U/kg nonacog beta pegol intravenous once weekly for prophylaxis.

Treatment of Bleeding Episodes
Bleeding episodes were treated as soon as they were identified. The dose for treatment of an uncomplicated mild/moderate bleeding episode, e.g. a joint bleed, was a single 40 U/kg dose. Severe bleeding episodes were treated immediately with 80 U/kg.

Surgery
Minor surgeries and placement of central venous access ports can be performed while participating in this trial by administering an additional 40 U/kg dose, or aligned to local practice after confirmation from sponsor's medical expert.

6.2.6 Sites and Centers

Of the 19 sites that screened subjects, 17 sites enrolled subjects. The study was therefore conducted at 17 sites in 8 countries, as follows: Canada (1), Germany (1), Italy (1), Japan (3), Malaysia (1), Taiwan (1), United Kingdom (3), United States (6).

6.2.7 Surveillance/Monitoring

Any event occurring after administration of nonacog beta pegol fulfilling the SAE (Serious Adverse Event) /MESI (Medical event of special interest) criteria had to be reported to Novo Nordisk within 24 hours. If one of the below mentioned stopping

criteria was fulfilled, enrollment of additional subjects was to be put on hold. All investigators were informed in writing. An urgent safety committee meeting would be called to decide whether the trial could continue with or without modifications. Dosing of subjects on treatment could continue while further evaluation of the SAE/MESI was made by the safety committee, unless otherwise decided by the safety committee. The evaluation of fulfilment of the below stopping rules by the safety committee took into consideration whether or not the subject was dosed according to protocol:

- Inhibitor formation (Bethesda Unit of ≥0.6 BU) in two subjects. A subject had inhibitor formation if the subject had been tested positive for inhibitors at two consecutive tests from the central laboratory.
- Anaphylaxis in two subjects after trial product administration.
- Occurrence of two significant thromboembolic events in two different subjects (e.g., myocardial infarction, pulmonary embolism, cerebral thrombosis/infarction).
- Death related to trial product assessed by Novo Nordisk or by the investigator.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint
Incidence of inhibitory antibodies against FIX defined as titer ≥0.6 BU over 52 weeks. Adequate safety with regard to inhibitors will be concluded if the observed rate is lower than or equal to 5%, corresponding to at most one subject with an observed inhibitor.

For the calculation of the rate, the numerator included the subjects with inhibitors, while the denominator included all subjects with a minimum of 10 EDs plus any subject with less than 10 EDs but with inhibitors.

Reviewer Comment: Please refer to my Reviewer Comment in Section 6.1.8 regarding the inhibitor rate calculation.

Secondary Endpoints
Efficacy endpoints
- Number of bleeding episodes during prophylaxis
- Hemostatic effect in treatment of bleeding episodes, which was assessed by the subject or parent(s)/caregiver and discussed with the investigator during visits to the trial site. The results are assessed using a 4-point categorical scale for hemostatic response (excellent, good, moderate and poor) defined as follows:
    o Excellent – abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single injection
    o Good – noticeable pain relief and/or improvement in signs of bleeding within 8 hours after a single injection
    o Moderate – probable or slight beneficial effect within the first 8 hours after the first injection but requiring more than one injection within 8 hours
    o Poor – no improvement, or worsening of symptoms within 8 hours after two injections

- FIX consumption described as frequency of dose/kg for prophylaxis use and number of doses and amount consumed for the treatment of bleeding episodes

Safety Endpoints
- AEs including SAEs and MESIs, and development of HCP antibodies

6.2.9 Statistical Considerations & Statistical Analysis Plan
Sample Size
No formal sample size calculations were performed.

Analysis Populations
- Full analysis set (FAS) – all subjects with efficacy data after exposure to nonacog beta pegol. All efficacy evaluations were conducted on the FAS.
- Safety analysis set – all subjects exposed to nonacog beta pegol. All safety evaluations were performed on this data set, except the primary endpoint analysis as noted in Section 6.2.8.

Analysis of the Endpoints`
The rate of neutralizing inhibitors was reported and a one-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution.
ABR was summarized and a 95% two-sided confidence interval was provided based on a Poisson regression model adjusting for exposure time and allowing for over-dispersion.

Summary statistics were provided for the other endpoints.

Missing Data
For the number of bleeding episodes per patient during routine prophylaxis, as a sensitivity analysis, data from subjects withdrawing prematurely (but after more than 1 month on prophylaxis) were imputed using the LOCF approach.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 28 subjects were screened for this study and 25 subjects were enrolled, of which 12 subjects were in the 0–6 year age group and 13 subjects were in the 7–12 years age group.

The safety analysis set and the full analysis set both consisted of all 25 dosed subjects. No subjects were excluded from any analysis.

6.2.10.1.1 Demographics
The trial population consisted of males with hemophilia B and a median age of 7.0 years (ranging from 1 to 12 years old); 12 subjects were in the age group of 0–6 years with a median age of 3.0, and 13 subjects were in the 7–12 years age group with a median age of 10.0 years. The mean weight of all subjects was 27.5 kg. The majority of the subjects

were White (52.0%) and the second-largest group was Asian (32.0%).Table 8 provides details on the demographics of the subjects.

Table 8. Baseline demographics (full analysis set)

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Age at baseline (years)			
N	12	13	25
Mean (SD)	3.1 (1.7)	9.6 (1.6)	6.5 (3.7)
Median	3.0	10.0	7.0
Min ; Max	1 ; 6	7 ; 12	1 ; 12
Country, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Canada	1 (8.3)	3 (23.1)	4 (16.0)
Germany	1 (8.3)	–	1 (4.0)
Italy	1 (8.3)	–	1 (4.0)
Japan	1 (8.3)	2 (15.4)	3 (12.0)
Malaysia	–	2 (15.4)	2 (8.0)
Taiwan	2 (16.7)	–	2 (8.0)
United Kingdom	3 (25.0)	–	3 (12.0)
United States of America	3 (25.0)	6 (46.2)	9 (36.0)
Ethnicity, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Hispanic or Latino	–	2 (15.4)	2 (8.0)
Not Hispanic or Latino	12 (100.0)	11 (84.6)	23 (92.0)
Race, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Asian	4 (33.3)	4 (30.8)	8 (32.0)
Black or African American	–	1 (7.7)	1 (4.0)
White	8 (66.7)	5 (38.5)	13 (52.0)
Other	–	3 (23.1)	3 (12.0)

Source: BLA 125611/0 (Module 5.3.5.2) report-body.pdf, table 10-3, page 88 of 455.

6.2.10.1.3 Subject Disposition
Of the 25 enrolled and exposed subjects, 24 subjects (96.0%) completed the main phase of the study (11 subjects in the 0–6 year age group and 13 subjects in the 7–12 years age group). One subject (0-6 years) withdrew during the main phase after 3.5 months with 10 EDs. Two subjects (7–12 years) withdrew at the end of main phase with >50 ED, and did not continue in the extension phase of the trial. No subjects withdrew during the extension phase before the cut-off date for the report (September 30, 2014).

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)
There is no primary efficacy endpoint. See Section 6.2.12.5 for the primary safety endpoint.

6.2.11.2 Analyses of Secondary Endpoints
ABR
Fifteen of the 25 subjects (60.0%) were treated for a total of 42 bleeds during the trial. The estimated mean ABR was 1.44 (95% CI: 0.92, 2.26) bleeds/subject/year; see Table 9.

Table 9. Annualized bleeding rate (full analysis set)

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total
Number of patients	12	13	25
Number of patients with bleeds, N(%)	5 (41.7)	10 (76.9)	15 (60.0)
Number of bleeds	11	31	42
Bleeds per patients (min ; max)	0.0 ; 3.0	0.0 ; 8.0	0.0 ; 8.0
Mean treatment period (years)	1.05	1.27	1.17
Individual ABRs			
N	12	13	25
Mean (SD)	0.83 (1.13)	1.96 (1.88)	1.42 (1.64)
Median	0.00	2.00	1.00
Min ; Max	0.00 ; 3.00	0.00 ; 6.51	0.00 ; 6.51
Poisson estimate of ABR	0.87	1.88	1.44
95% CI	0.38 ; 2.01	1.14 ; 3.09	0.92 ; 2.26

Based on a Poisson regression model with age group as a factor allowing over-dispersion and using treatment duration as an offset

Source: BLA 125611/0 (Module 5.3.5.2) report-body.pdf, table 11-2, page 102 of 455.

Hemostatic Response

The hemostatic efficacy of all 42 bleeding episodes requiring treatment was rated, of which 39 bleeding episodes had assessments of excellent or good. The overall success rate was 92.9%.; see Table 10.

Table 10. Hemostatic response (full analysis set)

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total
Number of patients	12	13	25
Number of patients with bleeds, N(%)	5 (41.7)	10 (76.9)	15 (60.0)
Number of bleeds	11	31	42
Haemostatic response, N(%)			
N	11 (100.0)	31 (100.0)	42 (100.0)
Excellent	7 (63.6)	15 (48.4)	22 (52.4)
Good	3 (27.3)	14 (45.2)	17 (40.5)
Moderate	0 (0.0)	2 (6.5)	2 (4.8)
Poor	1 (9.1)	0 (0.0)	1 (2.4)
Success/failure			
N	11 (100.0)	31 (100.0)	42 (100.0)
Success	10 (90.9)	29 (93.5)	39 (92.9)
Failure	1 (9.1)	2 (6.5)	3 (7.1)

Source: BLA 125611/0 (Module 5.3.5.2) report-body.pdf, table 11-7, page 105 of 455.

6.2.11.3 Subpopulation Analyses

ABR

The estimated ABR in the trial was 1.44 for the entire subject population, 1.88 in the 7–12 years age group and 0.87 for the 0–6 year age group (Table 9). Younger children had a numerically lower ABR than older children.

Table 11. ABR comparison by race

	Asian	Black/African American	White	Other
Number of subjects	8	1	13	3
Number of subjects with bleeds	4	1	7	3
Number of bleeds	13	3	22	4
Mean (median)	1.19 (0.68)	2.03 (2.03)	1.58 (1)	1.12 (0.69)
Min, Max	0, 4.11	2.03, 2.03	0, 6.51	0.68, 2
Poisson estimate of ABR	1.23	2.03	1.67	1.02
95% CI	0.52, 2.93	0.65, 6.29	0.85, 3.26	0.47, 2.22

Source: BLA 125611/0 Module 5.3.5.2 report-body_study3774.pdf 14.2.24 page170 of 1237

Hemostatic Response

Table 10 shows the hemostatic response by age group and Table 12 shows the response by race.

Table 12. Hemostatic response by race

Race	Asian (n=8)	Black/African American (n=1)	White (n=13)	Other (n=3)
Number of bleeds rated	13	3	22	4
Number of successes	13	2	20	4
Success rate	100%	66.7%	90.9%	100%

Source: BLA 125611/0 Module 5.3.5.2 report-body_study3774.pdf 14.2.42 page191 of 455

6.6.2.11.4 Dropouts and/or Discontinuations

All withdrawn subjects contributed data until the date of withdrawal. No subjects were withdrawn due to adverse events. The exposure time was included in the model as an offset variable to take care of unequal follow-up time and potentially missing data. Additional sensitivity analysis of the ABR using LOCF was also conducted, and these analysis results support the original analysis without the imputation.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No subjects died while participating in the study.

6.2.12.4 Nonfatal Serious Adverse Events

There was one SAE regarding food poisoning and was judged not to be related to nonacog beta pegol.

6.2.12.5 Adverse Events of Special Interest (AESI)

No subject had inhibitors detected. The one-sided 97.5% upper confidence limit is 0.16.

6.3 Trial #3

NN7999-3773 (Surgery Study)

6.3.1 Objectives (Primary, Secondary, etc.)

Primary objective: To evaluate the hemostatic effect of nonacog beta pegol during surgical procedures in subjects with hemophilia B.

Secondary objectives:
- To evaluate the general safety, including immunogenicity of nonacog beta pegol, when used for prevention and treatment of bleeding throughout the surgical period;
- To evaluate the hemostatic effect of nonacog beta pegol during the post-operative period**.**

6.3.2 Design Overview

The study was open-label, multicenter and uncontrolled, evaluating the efficacy and safety of nonacog beta pegol in major surgical procedures in subjects with hemophilia B. Subjects could be recruited from the pivotal study (NN7999-3747) or the extension study (NN7999-3775). In addition, new subjects could also be recruited into this study. After completion of the surgery study, subjects were offered to continue on prophylaxis or on-demand treatment in the extension study (NN7999-3775).

6.3.3 Population

The inclusion criteria were:
- Written informed consent from the subject or the child's parent/LAR obtained before any study-related activities. Study-related activities were any procedure that would not have been performed during normal management of the subject.
- Male subjects with moderately severe or severe congenital hemophilia B with a FIX activity ≤2% according to medical records.
- History of at least 150 EDs to other FIX products.
- Age 13-70 years (both inclusive).

- Body Mass Index (BMI) ≤35.
- Scheduled major surgery.
- The subject and/or LAR were capable of assessing a bleeding episode, keeping a diary, home treatment of bleeding episodes and otherwise capable of following the trial procedures.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Dose Adjustment

Upon confirmation of eligibility, the subject was dosed once with 40 U/kg nonacog beta pegol at the clinic. The FIX activity after 30 minutes at this visit, as measured by the central laboratory, was used to determine if dose adjustments were necessary during the peri-operative period.

Dosing Pre- and During Surgery

All subjects received a pre-operative dose of nonacog beta pegol 15 minutes to 4 hours prior to the surgery and before any procedures were undertaken including anesthesia. The pre-operative dose was a single bolus injection of 80 U/kg. Samples for FIX activity measurements were drawn post dose at 30 minutes (recovery), 4, 8 and 24 hours. If needed, the dose level of nonacog beta pegol could be adjusted to aim for a FIX activity level of approximately 1.0 U/mL and maintained during surgery according to WFH guidelines.

Dosing During the Post-Operative Period

It was recommended to give a dose of 40 U/kg 24-48 hours after the pre-operative dose depending on the desired FIX activity level. From the day after surgery (Day 1) and through Day 6, nonacog beta pegol dosing was adjusted to aim for a FIX activity level of approximately 0.50 U/mL. This most likely meant a dose of 40 U/kg approximately 48-72 hours after the pre-operative dose. It was likely that the pre-operative dose of 80 U/kg and the two doses of 40 U/kg in the post-operative period until and through Day 6 were sufficient, but it was monitored locally by daily measurements of FIX activity using the nonacog beta pegol reference standard as long as the subject was hospitalized, in open-admission or in out-patient settings.

6.3.6 Sites and Centers

Ten sites in eight countries enrolled subjects. The eight countries were: Italy (1), Malaysia (1), Romania (1), South Africa (1), Taiwan (1), Turkey (1), United Kingdom (2), US (2).

6.3.8 Endpoints and Criteria for Study Success

Primary Endpoint

Hemostatic response was evaluated by the surgeon, anesthesiologist and/or Investigator based on experience immediately after surgery (last stitch) using a four-point response scale: Excellent, good, moderate, or poor.

- Excellent: Better than expected/predicted in this type of procedure
- Good: As expected in this type of procedure

- Moderate: Less than optimal for the type of procedure but homeostatic response maintained without change of treatment regimen
- Poor: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required

Treatment success during surgery was defined as excellent or good outcomes while treatment failure was defined as moderate or poor outcomes.

Secondary Endpoints include:

Efficacy endpoints

- Hemostatic effect during surgery:
  – Consumption of nonacog beta pegol (U/kg) during surgery.
  – Transfusion requirements (fulfilling transfusion criteria) during surgery.
  – Hemoglobin pre and post-surgery start (0, 1 and 24 h).
- Hemostatic effect in the post-operative period, through Day 6:
  – Consumption of nonacog beta pegol (U/kg) during post-operative period through Day 6.
  – Transfusion requirements (fulfilling transfusion criteria) during post-operative period through Day 6.
  – Hemoglobin.
  – Drainage volume.
  – Wound hematoma.
- Hemostatic effect of nonacog beta pegol during the post-operative period, Days 7 through Day 13, if the subject is still hospitalized:
  – Consumption of nonacog beta pegol (U/kg), during time period Day 7 through Day 13.
  – Transfusion requirements (fulfilling transfusion criteria), during time period Day 7 through Day 13.
  – Hemoglobin.
  – Drainage volume.
  – Wound hematoma.

Safety Endpoints

- AEs and SAEs reported during the trial period.
- Development of inhibitors against FIX ($\geq$0.6 BU).

No study success criterion is specified for any of the study endpoints.

6.3.9 Statistical Considerations & Statistical Analysis Plan

The study planned for 16 screened subjects and 5-10 subjects to complete the trial. The study sample size was determined based on recommendations in the EMA draft guideline on the clinical investigation of recombinant and human plasma-derived Factor IX products.

The full analysis set and the safety analysis set both consist of all subjects exposed to nonacog beta pegol.

Both primary efficacy and secondary endpoints were summarized using descriptive statistics.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed
The full analysis set and the safety analysis set both consist of all 13 dosed subjects.

6.3.10.1.1 Demographics
The trial population consisted of males with a median age of 39 years (ranging from 15 to 56 years old). Of the 13 exposed subjects, one subject was adolescent (15 years old), while the remaining subjects were adults (≥18 years old). The median weight was 71.0 kg (ranging from 52.0 to 104.4 kg). The majority of the subjects were White (8/13; 61.5%) while 3 (23.1%) were Asian and 2 (15.4%) were Black or African American.

6.3.10.1.3 Subject Disposition
A total of 15 subjects were screened. Two subjects were screening failures and 13 subjects were dosed with nonacog beta pegol. Of the two screening failures, one subject met an exclusion criterion while the other subject decided to postpone the surgery to a later date. All 13 dosed subjects completed the trial. Of the 13 subjects, 6 were new subjects, 2 were also participants in the pivotal trial (NN7999-3747) and 5 were also participants in the extension trial (NN7999-3775). Each of the 13 subjects had one surgery.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)
The hemostatic effect of nonacog beta pegol was rated as 'excellent' in 10 of the 13 (76.9%) surgeries and as 'good' in 3 (23.1%) surgeries. Thus, the success rate was 100%.

6.3.11.3 Subgroup Analyses
No subgroup analyses were conducted since the primary endpoint success rate was 100%.

6.3.11.4 Dropouts and/or Discontinuations
Two subjects withdrew from the study due to screen failure and were not included in the analysis.

6.3.12 Safety Analyses

6.3.12.3 Deaths
No subjects died while participating in the study.

6.3.12.4 Nonfatal Serious Adverse Events
There were no SAEs.

6.3.12.5 Adverse Events of Special Interest (AESI)

No subjects were detected to have FIX inhibitors and no thromboembolic events occurred.

6.4 Trial #4

NN7999-3775 (Extension Study)

6.4.1   Objectives (Primary, Secondary, etc.)

Primary objective: To evaluate the immunogenicity of nonacog beta pegol

Secondary objectives included:

- To evaluate clinical efficacy of hemostasis (treatment of bleeding episodes) of nonacog beta pegol
- To evaluate clinical efficacy of nonacog beta pegol in long term bleeding prophylaxis (number of bleeding episodes during prophylaxis)
- To evaluate the efficacy of nonacog beta pegol by the surrogate marker for efficacy, FIX activity
- To evaluate general safety of nonacog beta pegol

6.4.2 Design Overview

The study was open label, non-randomized and multi-national with the purpose of evaluating safety and clinical efficacy of treatment of bleeding episodes, and for long-term prophylaxis with nonacog beta pegol. Subjects could be recruited from the pivotal study (NN7999-3747) or the surgery study (NN7999-3773).

The study included four different treatment arms: initially two prophylaxis treatment arms with 10 or 40 U/kg nonacog beta pegol, and one on-demand treatment with 40 U/kg. The third prophylaxis option of 80 U/kg nonacog beta pegol dosed every two weeks was added in amendment 14 (dated March 22, 2012) to the protocol. Surgery was allowed during this study.

Eligible subjects received nonacog beta pegol as prophylaxis or as on-demand treatment. The choice of treatment was agreed between the subject and the investigator and could be changed throughout the trial. In most cases, nonacog beta pegol was administered at home, except when subjects on prophylaxis were attending a visit at the clinic. In this case, nonacog beta pegol was administered at the clinic to allow for both pre- and post-dose blood samples and assessments. The subjects initially attended the clinic every three months, reducing to every six months after Visit 5.

6.4.3 Population

Subjects with hemophilia B, aged 13-70 years and a FIX activity of $\leq 2\%$ were enrolled.

Other inclusion criteria included:
- Informed consent obtained before any study-related activities. Study-related activities are any procedure that would not have been performed during normal management of the subject
- Previous participation in NN7999-3747 or NN7999-3773
- The subject and/or LAR is capable of assessing a bleeding episode, keeping a diary, home treatment of bleeding episodes and otherwise capable of following the trial procedures

6.4.4 Study Treatments or Agents Mandated by the Protocol

Subjects were free to switch between the four treatment arms if agreed between the investigator and the subject: 10 U/kg, 40U/kg, 80 U/kg and on demand. Subjects could start and stop the 80 U/kg treatment at an unscheduled visit if there was more than one month remaining to the next scheduled visit. Subjects with on-demand treatment and subjects on prophylaxis who experienced a bleeding episode were to treat the bleeding episode with a single dose of 40 U/kg, unless the bleeding episode was severe in which case it was to be treated with 80 U/kg.

6.4.6 Sites and Centers
The study was conducted at 41 sites in 15 countries as follows: France (1 site); Germany (3); Italy (2); Japan (4); Macedonia (2); Malaysia (1); Netherlands (1); Romania (1); Russia (1) site; South Africa (1); Taiwan (1); Thailand (2); Turkey (3); United Kingdom (5); United States (13).

6.4.8 Endpoints and Criteria for Study Success
Primary Endpoint: Incidence of inhibitory antibodies against FIX defined as titre ≥ 0.6 BU

Secondary Efficacy Endpoints
- Hemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes

  The assessment of hemostatic response was made by the subject or LAR using a four-point scale. The four-point scale was defined as below and took into account the improvement in signs of bleeding, mainly by pain relief, as well swelling and motion. The evaluation was to reflect the hemostatic response from the time of treatment and until eight hours after the treatment had been administered.
  - Excellent – abrupt pain relief and/or clear improvement in objective signs of bleeding within eight hours after a single injection
  - Good – noticeable pain relief and/or improvement in signs of bleeding within hours after a single injection
  - Moderate – probable or slight beneficial effect within the first eight hours after the first injection but requiring more than one injection within eight hours
  - Poor – no improvement, or worsening of symptoms within eight hours after two injections

- Number of bleeding episodes per subject during routine prophylaxis
- FIX trough levels
- The number of injections required per bleeding episode
- Amount of nonacog beta pegol required per bleeding episode (U/kg BW/bleeding episode)

Secondary Safety Endpoints
- AEs and SAEs
- HCP antibodies
- General safety endpoints including laboratory parameters, physical examination and vital signs

6.4.9 Statistical Considerations & Statistical Analysis Plan

Sample size was determined by the number of subjects included in the previous studies (NN7999-3747 and NN7999-3773). A minimum of 50 subjects were planned to complete the trial.

The safety analysis set and the full analysis set both include all the subjects exposed to nonacog beta pegol. Safety was analyzed on the safety analysis set and efficacy was analyzed on the full analysis set

The primary endpoint and the clinical efficacy parameters were summarized using descriptive statistics. The number of bleeding episodes for subjects following the same treatment arm for at least 3 months was analyzed by a Poisson regression model with treatment group as a factor. The model allowed for over-dispersion and had treatment duration as offset.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

The safety analysis set and the full analysis set both consisted of all 71 dosed subjects. No subjects were excluded from any analysis**.**

6.4.10.1.1 Demographics
The all-male study population had a median (range) age of 32 (14-66) years. The median (range) weight was 75.3 (46.0–104.4) kg. The majority of the subjects were White (48/71; 67.6%) while 21.1% were Asian, 7.0% were Black or African American, and 4.2% were listed as "other".

6.4.10.1.3 Subject Disposition
No screening failures were reported for the 71 recruited subjects. Six of the 71 subjects withdrew from the study. Of the 65 subjects who completed the trial, 48 subjects were treated on the 40 U/kg prophylaxis treatment arm at some point during the trial, 18 subjects were treated on the 10 U/kg prophylaxis arm and 5 subjects were in the on demand group.

Details on the six subjects who withdrew from the trial are the following:
- Subject (b) (6) and (b) (6) (both 40 U/kg/week) due to withdrawal criteria number: incapacity or unwillingness to follow the trial procedures.
- Subject (b) (6) and (b) (6) due to "other", i.e. lost to follow-up (both on 10 U/kg/week),
- Subject (b) (6) due to ineffective therapy (40 U/kg/week). This subject had no neutralizing or binding antibodies to nonacog beta pegol.
- Subject (b) (6) (40 U/kg/week) due to death (AE), not associated with nonacog beta pegol exposure.

A total of 14 subjects underwent surgery during the trial: four subjects in the 10 U/kg prophylaxis dose arm and 10 subjects in the 40 U/kg prophylaxis dose arm.

6.4.11 Efficacy Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

There is no primary efficacy endpoint. See Section 6.4.12.5 for the primary safety endpoint analysis.

6.4.11.2 Analyses of Secondary Endpoints

A total of 207 bleeding episodes were reported for the 71 subjects; two bleeding episodes were missing the response assessment. The hemostatic responses were rated as a success for 194 of the bleeding episodes with the response assessment, with a success rate of 94.6% (194/205).

The estimated mean ABR based on the Poisson regression analysis is 2.7 (95% CI: 1.95, 3.73).

6.4.11.4 Dropouts and/or Discontinuations

Six subjects withdrew from the trial due to withdrawal criteria, death or other reasons. Sensitivity analysis of the hemostatic response including the two missing responses as failure was conducted and the results support the primary analysis results.

6.4.12 Safety Analyses

6.4.12.3 Deaths

One death (hepatocellular carcinoma, subject (b) (6), 40 U/kg prophylaxis treatment arm) was reported. The subject was diagnosed with metastatic stage IV after 17 EDs of nonacog beta pegol. The subject had a history of hepatitis B and C and hepatic cirrhosis and was therefore evaluated to have had a higher risk of development of hepatocellular carcinoma. This event was judged by the investigator as not likely to be related to nonacog beta pegol exposure.

6.4.12.4 Nonfatal Serious Adverse Events

There were five nonfatal SAEs in five subjects: road traffic accident, faecaloma, local swelling, gastroenteritis, and femur fracture.

6.4.12.5 Adverse Events of Special Interest (AESI)

No subject developed inhibitory antibodies against nonacog beta pegol during the study, and no thromboembolic event was reported.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Hemostatic Efficacy
A pooled analysis of hemostatic response, which includes all bleeds from all treatment arms in the pivotal (study 3747, n=341), pediatric (study 3774, n=42), surgery (study 3773, n=3) and extension (study 3775, n=205) studies, is presented in Table 13 below:

Table 13. Efficacy in treatment of bleeding episodes in previously treated subjects

New Bleeding Episodes	n = 597
Hemostatic response success rate*	
Excellent or Good	551 (93.2%)
Moderate or Poor	40 (6.8%)
Number of injections to treat a bleeding episode	
1 injection	521 (87.3%)
2 injections	60 (10.1%)
>2 injections	16 (2.7%)

*Hemostatic response rate based on 591 evaluated bleeding episodes (data missing for six bleeding episodes).
Source: BLA 125611/0 module 1.14.1 annotated-draft-labeling-text.doc table 10.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

No major statistical issues were identified during the review of this BLA. The sponsor submitted study reports for four clinical studies, including a pivotal study, a pediatric study, a surgery study and an extension study. This review evaluated the four studies, and the results from the primary and secondary endpoint analyses of those four studies are the following.
1. The primary endpoint in studies 3747, 3774 and 3775 was incidence of inhibitory antibodies (inhibitors) against FIX. There were no inhibitory antibodies detected in any of the subjects in the three studies, nor in the surgery study (study 3773).
2. For the pivotal study (study 3747), the hemostatic response rate for the treatment and control of bleeding episodes for subjects in both the prophylaxis treatment and on-demand treatment groups is 92.2% (95% CI: 86.9; 95.4), which meets the success criteria. Based on a Poisson regression analysis, the estimated mean ABR for 40 U/kg once weekly prophylaxis subjects is 2.51 [95% CI: 1.42; 4.43]),

which meets the success criteria. For the pediatric study (study 3774), the estimated mean ABR was 1.44 (95% CI: 0.92, 2.26) bleeds/subject/year. The hemostatic efficacy of all 42 bleeding episodes requiring treatment was rated, of which 39 bleeding episodes had assessments of excellent or good. The overall success rate was 92.9%.

3. The success rate of hemostatic effect of nonacog beta pegol was 100% (13/13) for the surgery study (study 3773).

4. A 42-year old subject in the extension study (study 3775) was diagnosed with metastatic stage IV hepatocellular carcinoma after 499 days in the trial program and died after 570 days. The event was evaluated as unlikely to be related to nonacog beta pegol and consequently, there were no SAEs with fatal outcome considered related to nonacog beta pegol in the completed studies.

10.2 Conclusions and Recommendations

The submission includes four completed clinical studies on previously treated subjects. None of the subjects in any of the studies developed inhibitory antibodies. In the pivotal study, the hemostatic response rate for subjects on both prophylaxis treatment and on-demand treatment groups, and the estimated mean annualized bleeding rate for 40 U/kg once weekly prophylaxis subjects, met their respective success criteria. There was one death during all the completed studies, but it is evaluated as unlikely related to nonacog beta pegol. There were no statistical issues identified during the review of this BLA, and the data support the proposed indications.