

Application Type	Original Application
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Division / Office	DHRR /OBRR
Priority Review	No
Reviewer Name(s)	Megha Kaushal
Review Completion Date / Stamped Date	May 30, 2017
Supervisory Concurrence	
Applicant	Novo Nordisk Inc.
Established Name	Coagulation Factor IX (Recombinant), GlycoPEGylated
(Proposed) Trade Name	REBINYN
Pharmacologic Class	Recombinant Full Length
Formulation(s), including Adjuvants, etc	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder in Single Use Vials containing 500, 1000, or 2000 IU for intravenous use after reconstitution
Dosing Regimen	On-demand treatment and control of bleeding episodes: 40 IU/kg body weight for minor and moderate bleeds, and 80 IU/kg body weight for major bleeds; Perioperative management: Pre-operative dose of 40 IU/kg body weight for minor surgery, and 80 IU/kg body weight for major surgery.
Indication(s) and Intended Population(s)	Perioperative management of hemophilia B subjects, {All Age Groups}; Control and prevention of bleeding episodes in hemophilia B subjects, {All Age Groups}
Orphan Designated (Yes/No)	Yes for Routine Prophylaxis; No for On Demand and Perioperative Management

**TABLE OF CONTENTS**

<b>GLOSSARY .....</b>	<b>1</b>
<b>1. EXECUTIVE SUMMARY .....</b>	<b>1</b>
1.1 Demographic Information: Subgroup Demographics and Analysis Summary.....	4
<b>2. CLINICAL AND REGULATORY BACKGROUND .....</b>	<b>4</b>
2.1 Disease or Health-Related Condition(s) Studied .....	4
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s).....	5
2.3 Safety and Efficacy of Pharmacologically Related Products .....	6
2.4 Previous Human Experience with the Product (Including Foreign Experience) .....	6
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission ....	6
2.6 Other Relevant Background Information.....	6
<b>3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES .....</b>	<b>7</b>
3.1 Submission Quality and Completeness .....	7
3.2 Compliance with Good Clinical Practices and Submission Integrity.....	7
3.3 Financial Disclosures .....	7
<b>4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>7</b>
4.1 Chemistry, Manufacturing, and Controls .....	7
4.2 Assay Validation.....	8
4.3 Nonclinical Pharmacology/Toxicology .....	8
4.4 Clinical Pharmacology.....	9
4.4.1 Mechanism of Action .....	9
4.4.2 Human Pharmacodynamics (PD).....	9
4.4.3 Human Pharmacokinetics (PK) .....	9
4.5 Statistical.....	9
4.6 Pharmacovigilance.....	10
<b>5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW ...</b>	<b>10</b>
5.1 Review Strategy .....	10
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review.....	10
5.3 Table of Studies/Clinical Trials.....	10
5.4 Consultations .....	12
5.4.1 Advisory Committee Meeting.....	12
5.4.2 External Consults/Collaborations .....	13
5.5 Literature Reviewed (if applicable).....	13
<b>6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS .....</b>	<b>13</b>
6.1 Trial #1: NN7999-3747.....	13
Initiated: April 29, 2011 Trial Completed: April 2, 2013 .....	13
6.1.1 Objectives (Primary, Secondary, etc.).....	13
6.1.2 Design Overview .....	13
6.1.3 Population.....	14
6.1.4 Study Treatments or Agents Mandated by the Protocol .....	15
6.1.5 Directions for Use .....	15
6.1.6 Sites and Centers .....	15
6.1.7 Surveillance/Monitoring .....	16
6.1.8 Endpoints and Criteria for Study Success.....	18
6.1.9 Statistical Considerations & Statistical Analysis Plan .....	19
6.1.10 Study Population and Disposition.....	19
6.1.11 Efficacy Analyses .....	21

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6.1.12 Safety Analyses.....	25
6.1.13 Study Summary and Conclusions .....	29
6.2 Trial #2: Trial NN7999-3773.....	30
6.2.1 Objectives.....	30
6.2.2 Design Overview .....	30
6.2.3 Population.....	31
6.2.4 Study Treatments or Agents Mandated by the Protocol .....	32
6.2.5 Directions for Use .....	32
6.2.7 Surveillance/Monitoring .....	32
6.2.8 Endpoints and Criteria for Study Success.....	33
6.2.9 Statistical Considerations & Statistical Analysis Plan .....	33
6.2.10 Study Population and Disposition.....	33
6.2.11 Efficacy Analyses .....	34
6.2.12 Safety Analyses.....	36
6.3.1 Objectives.....	39
6.3.2 Design Overview .....	39
6.3.3 Population.....	40
6.3.4 Study Treatments or Agents Mandated by the Protocol .....	40
6.3.5 Directions for Use .....	40
6.3.6 Sites and Centers.....	41
6.3.7 Surveillance/Monitoring .....	41
6.3.8 Endpoints and Criteria for Study Success.....	41
6.3.9 Statistical Considerations & Statistical Analysis Plan .....	41
6.3.10 Study Population and Disposition.....	42
6.3.11 Efficacy Analyses .....	43
6.3.12 Safety Analyses.....	46
6.4.1 Objectives.....	48
6.4.2 Design Overview .....	49
6.4.3 Population.....	49
6.4.4 Study Treatments or Agents Mandated by the Protocol .....	49
6.4.5 Directions for Use .....	49
6.4.6 Sites and Centers.....	50
6.4.7 Surveillance/Monitoring .....	50
6.4.8 Endpoints and Criteria for Study Success.....	50
6.4.9 Statistical Considerations & Statistical Analysis Plan .....	50
6.4.10 Study Population and Disposition.....	50
6.4.11 Efficacy Analyses .....	51
6.4.12 Safety Analyses.....	53
<b>7. INTEGRATED OVERVIEW OF EFFICACY.....</b>	<b>54</b>
7.1 Indication #1 On-Demand Treatment and Control of Bleeding Episodes.....	55
7.1.1 Methods of Integration.....	55
7.1.2 Demographics and Baseline Characteristics.....	55
7.1.3 Subject Disposition .....	55
7.1.4 Analysis of Primary Endpoint(s) .....	56
7.1.5 Analysis of Secondary Endpoint(s) .....	56
7.1.6 Other Endpoints.....	56
7.1.7 Subpopulations.....	56
7.1.8 Persistence of Efficacy .....	56
7.1.9 Product-Product Interactions.....	56
7.1.10 Additional Efficacy Issues/Analyses .....	56
7.1.11 Efficacy Conclusions .....	56
7.2 Indication #2.....	57
7.2.1 Methods of Integration.....	57
7.2.2 Demographics and Baseline Characteristics.....	57

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7.2.3 Subject Disposition .....	57
7.2.4 Analysis of Primary Endpoint(s) .....	57
7.2.5 Analysis of Secondary Endpoint(s) .....	57
7.2.6 Other Endpoints.....	57
7.2.7 Subpopulations.....	57
7.2.8 Persistence of Efficacy .....	58
7.2.9 Product-Product Interactions .....	58
7.2.10 Additional Efficacy Issues/Analyses .....	58
7.2.11 Efficacy Conclusions .....	58
7.3 Indication #3.....	58
7.3.1 Methods of Integration.....	58
7.3.2 Demographics and Baseline Characteristics.....	58
7.3.3 Subject Disposition .....	58
7.3.4 Analysis of Primary Endpoint(s) .....	58
7.3.5 Analysis of Secondary Endpoint(s) .....	58
7.3.6 Other Endpoints.....	59
7.3.7 Subpopulations.....	59
7.3.8 Persistence of Efficacy .....	59
7.3.9 Product-Product Interactions .....	59
7.3.10 Additional Efficacy Issues/Analyses .....	59
7.3.11 Efficacy Conclusions .....	59
<b>8. INTEGRATED OVERVIEW OF SAFETY .....</b>	<b>59</b>
8.1 Safety Assessment Methods .....	59
8.2 Safety Database.....	60
8.2.1 Studies/Clinical Trials Used to Evaluate Safety .....	60
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations .....	60
8.2.3 Categorization of Adverse Events .....	60
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials.....	60
8.4 Safety Results .....	60
8.4.1 Deaths .....	60
8.4.2 Nonfatal Serious Adverse Events.....	61
8.4.3 Study Dropouts/Discontinuations .....	61
8.4.4 Common Adverse Events .....	61
8.4.5 Clinical Test Results .....	61
8.4.6 Systemic Adverse Events.....	61
8.4.7 Local Reactogenicity .....	61
8.4.8 Adverse Events of Special Interest .....	61
8.5 Additional Safety Evaluations .....	62
8.5.1 Dose Dependency for Adverse Events .....	62
8.5.2 Time Dependency for Adverse Events .....	62
8.5.3 Product-Demographic Interactions.....	63
8.5.4 Product-Disease Interactions .....	63
8.5.5 Product-Product Interactions .....	63
8.5.6 Human Carcinogenicity .....	63
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound .....	63
8.5.8 Immunogenicity (Safety).....	63
8.6 Safety Conclusions .....	63
<b>9. ADDITIONAL CLINICAL ISSUES .....</b>	<b>64</b>
9.1 Special Populations.....	64
9.1.1 Human Reproduction and Pregnancy Data.....	64
9.1.2 Use During Lactation .....	64
9.1.3 Pediatric Use and PREA Considerations .....	64

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9.1.4 Immunocompromised Subjects .....	64
9.1.5 Geriatric Use .....	64
9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered .....	64
<b>10. CONCLUSIONS .....</b>	<b>64</b>
<b>11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS .....</b>	<b>65</b>
11.1 Risk-Benefit Considerations .....	65
11.2 Risk-Benefit Summary and Assessment .....	68
11.3 Discussion of Regulatory Options .....	68
11.4 Recommendations on Regulatory Actions .....	68
11.5 Labeling Review and Recommendations .....	68
11.6 Recommendations on Postmarketing Actions .....	68

**TABLES:**

Table 1 Baseline Demographics: .....	4
Table 2: Approved FIX products .....	5
Table 3: BIMO Inspection Sites .....	7
Table 4: Clinical Trials: .....	10
Table 5: Trial 3747 Monitoring .....	16
Table 6: Protocol Deviations .....	19
Table 7: Demographics .....	19
Table 8: Details of Bleeds .....	21
Table 9: Hemostatic Response and Success Rate- Full Analysis Set .....	22
Table 10: Annualized Bleeding Rate .....	23
Table 11: Spontaneous and Traumatic Bleeds .....	23
Table 12: Adverse Events with Probable Relation .....	27
Table 13: Serious Adverse Events .....	27
Table 14: Minor Surgeries .....	34
Table 15: Major Surgeries .....	34
Table 16: Adverse Events .....	37
Table 17: Demographics of Pediatric Trial .....	42
Table 18: Protocol Deviations .....	43
Table 19: Details of Bleeds .....	44
Table 20: Annualized Bleeding Rate .....	44
Table 21: Hemostatic Response and Success Rate- Full Analysis Set .....	45
Table 22: Number of Bleeds .....	45
Table 23: Annualized Bleeding Rate .....	51
Table 24: Baseline Demographics .....	55
Table 25: Duration of Exposure .....	60
Table 26: Adverse Events of Special Interest .....	61
Table 27: Benefit Risk .....	67

**FIGURES:**

Figure 1: Trial 3747 Design Overview .....	14
Figure 2: Trial Sites .....	15
Figure 3: Subject Disposition .....	20
Figure 4: Design Overview .....	30
Figure 5: Design Overview .....	39
Figure 6: Design Overview .....	49

## GLOSSARY

ABR	Annualized Bleeding Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
aPTT	activated partial thromboplastin time
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BU	Bethesda Unit
CHO	Chinese hamster ovary
CI	Confidence Interval
CMC	Chemistry, manufacturing, and controls
CRF	case report form
eCTD	Electronic Common Technical Document
ED	Exposure Day
GCP	Good Clinical Practices
IU	International Units
PK	Pharmacokinetic
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
PVP	Pharmacovigilance Plan
rFIX	recombinant coagulation factor IX
SAE	Serious Adverse Event
SOC	system organ class
T <sub>1/2</sub>	half-life
TEAE	treatment emergent adverse event
V <sub>z</sub>	volume of distribution
WFH	World Federation of Hemophilia

### 1. Executive Summary

Factor IX (FIX) deficiency (hemophilia B, Christmas disease) is the second most common coagulation factor deficiency. Hemophilia B is often divided into groups by factor level correlating with the disease pattern. A goal of modern hemophilia management is to prevent spontaneous bleeds, by supplying replacement factor that will maintain FIX activity levels to a value of >1-5%, i.e., in the range of subjects with the moderate form of the disease.

REBINYN (Antihemophilic Factor [Recombinant], polyethylene glycol [PEG]); rFIX-PEG; or N9-GP is a recombinant FIX molecule expressed in a genetically engineered Chinese hamster ovary cell line. A 40 kiloDalton (kDa) PEG moiety is attached to the FIX which increases the half-life of the protein. As a result, REBINYN is longer-acting and was developed for intravenous replacement therapy or prophylaxis on a less frequent basis than standard regimens in subjects with hemophilia B. The elimination mean half-life of REBINYN is 93 hours compared to an average half-life of 20-30 hours in other plasma derived and recombinant FIX products. Recent development of FIX products includes two other new longer acting products with half-lives of 80-100 hours.

This original BLA seeks the following indications for adults and children: a) on-demand treatment and control of bleeding b) routine prophylaxis for the treatment of bleeding episodes and c) for perioperative management. The basis to support licensure for the proposed indications for REBINYN are as follows: a) Trial 3747- data from a phase 3 trial in adolescents and adults b) Trial 3773- data from a surgery trial in adolescent and adults c) Trial 3774- data from a pediatric trial d) Trial 3775- data from an extension trial in adolescents and adults.

Trial 3747 was a phase 3 multicenter, randomized study to evaluate the PK, efficacy, safety and immunogenicity of REBINYN in 74 adult and adolescent subjects to support routine prophylaxis and on demand treatment. Subjects were randomized to once weekly prophylactic treatment with either 10 IU/kg or 40 IU/kg of REBINYN over a period of 12 months or at least 50 exposure days (EDs). A subset of subjects underwent a PK evaluation prior to the start of prophylactic treatment. The primary objective was to assess the incidence of FIX inhibitory antibodies ( $\geq 0.6$  Bethesda units [BU] using the Nijmegen modification of the Bethesda assay). No subject developed inhibitory antibodies to FIX. There were 215 adverse events (AEs) in 60 subjects. Four serious AEs (SAEs) were reported, judged not to be related to the study drug. No subjects were withdrawn due to AEs. There were no deaths reported. There was a total of 345 bleeds in 55 subjects. The majority of bleeds were treated by one injection (87%); 10.4% were resolved with two injections and 2.6% were solved with  $\geq 3$  injections. The success rate for all bleeds was 92.4% (95% CI: 87.0; 95.6), which was above the pre-specified success rate of 80%. The total median annualized bleeding rate (ABR) [Interquartile Range (IQR)] was 2.93 [0.99; 6.02] for the 10 IU/kg group and 1.04 [0; 4] for the 40 IU/kg group. For the statistical analysis, clinical efficacy of the study drug was assessed by testing if the randomized doses led to bleeding rates below 4.8 (60% reduction in the estimated ABR of 12 for on-demand subjects). The estimated ABR was 4.56 (95% Confidence Interval [CI]: 3.01; 6.90) in the 10 IU/kg arm and 2.51 (95% CI: 1.42; 4.43) in the 40IU/kg arm. A prophylactic protection with 40IU/kg once weekly was demonstrated statistically, while prophylactic protection with 10IU/kg once weekly was not demonstrated statistically. Approximately half (48.6%) of the bleeds in the 40 IU/kg group were spontaneous bleeds, despite reaching trough levels of 40%. More than half (56%) of the spontaneous bleeds involved a target joint in the 40 IU/kg group. The total median ABR for spontaneous bleeds was 0 [0; 2.1]. The estimated ABR for spontaneous bleeds was 2.2 (95% CI: 1.35; 3.57). The study drug demonstrated efficacy in this trial.

Trial 3773 was a phase 3, multicenter, open label, study to evaluate safety and efficacy during major surgical procedures in 13 adult and adolescents. Subjects received 80 IU/kg prior to the procedure and 40 IU/kg, if needed post operatively. Nine of the 13 procedures were evaluated as major procedures and four were minor. Perioperative hemostatic efficacy was rated as excellent for ten surgeries and good for three surgeries. Postoperative blood loss was observed in seven subjects. No deaths were reported and no related serious adverse events occurred. REBINYN was shown to be safe and tolerated. The study drug demonstrated hemostatic efficacy in both major and minor surgeries, although there was a limited amount of subjects in the study.

Trial 3774 was a phase 3, multicenter, open-label, study evaluating PK, safety, efficacy of REBINYN when used for routine prophylaxis and treatment of breakthrough bleeding episodes in 25 children with hemophilia B (FIX activity  $\leq 2\%$ ). Subjects received once weekly prophylactic dosing with 40 IU/kg of REBINYN over a period of 12 months or at least 50 EDs. A subset of subjects underwent a PK evaluation prior to the start of

prophylactic treatment. The primary objective was to assess the incidence of FIX inhibitory antibodies ( $\geq 0.6$  Bethesda units [BU] using the Nijmegen modification of the Bethesda assay). No subject developed inhibitory antibodies to FIX. There were 250 AEs in 23 subjects. One serious AE was reported in one subject and not judged to be related to the study drug. No subjects were withdrawn due to AEs. There were no reported deaths. Fifteen subjects were treated for a total of 42 bleeds during the trial. In the older age group, 10 subjects experienced bleeds requiring treatment, whereas there were 5 subjects in the younger age group. Twenty-five of the bleeds were traumatic (60%), 13 were spontaneous (31%), and 4 were classified as of other origin (10%). All of the 42 bleeds were rated for hemostatic response with a success rate of 92.9%. The majority of bleeds were resolved with 1 injection in both age groups. The total median ABR [IQR] was 1.0 [0; 2.1]. The estimated ABR was 1.44 (95% CI: 0.92; 2.26). Approximately one-third (31%) of the bleeds were spontaneous bleeds. The total median ABR for spontaneous bleeds was 0 [0; 0]. The estimated ABR for spontaneous bleeds was 0.45 (95% CI: 0.18; 1.08). The study drug demonstrated efficacy in this trial.

Although REBINYN demonstrated efficacy, a preclinical finding of concern was noted during this review. Specifically, the nonclinical studies indicated PEG accumulation in the choroid plexus and vacuolation resulting from repeat REBINYN dosing in nonclinical studies. This finding in nonclinical studies raises concerns regarding the clinical implications of REBINYN use in humans. The clinical implications are unknown at this time. No clear safety signal that could be attributed to the accumulation of PEG was observed in the clinical trials. Upon review of the data, it is unclear whether monitoring of neurologic function in the clinical studies was adequate to detect all clinically important neurologic signs or symptoms. In addition, it is unclear whether the size of the safety database (i.e., number of adult and/or pediatric subjects exposed to the product; duration of follow-up of those subjects) was sufficient to assess the safety of the product. Due to these uncertainties, a Blood Product Advisory Committee (BPAC) was held on April 4<sup>th</sup>, 2017. Based on their discussion, the majority of the AC members suggested a postmarketing study to be conducted which would assess neurologic and neurocognitive parameters in a standardized approach. The particular metrics in these assessments were not discussed by the committee or by the applicant. Some of the committee members recommended restricting the routine prophylaxis indication to only pediatric subjects above 2 years of age, while others stated that an arbitrary age cut offs should not be used. All of the committee members agreed that short-term use (on demand treatment and perioperative use) of the study drug was not concerning. The committee members agreed that premarketing approval studies would be useful; however, postmarketing studies may be sufficient to collect more safety data with respect to neurocognitive function in patients.

Based on the review of the submitted clinical data, discussion at the BPAC, discussion with the entire review team, and with CBER upper management, the recommendation for this original biologic application is to approve the following indications for all age groups:

- a) on-demand treatment and control of bleeding
- b) perioperative management.

The routine prophylaxis indication is blocked by exclusivity by another FIX product until 2020. Due to the potential neurocognitive function concerns raised by the nonclinical data, a plan for collection of postmarketing safety data will be requested under the IND and the data will need to be reviewed prior to approving this indication.



### 1.1 Demographic Information: Subgroup Demographics and Analysis Summary

All subjects were male. The median age was 23 years from all the studies. The baseline demographics from Trials 3747, 3773, and 3774 are below.

Table 1 Baseline Demographics:

	0-6 years	7-12 years	13-17 years	18-70 years	Total
Number of patients	12	13	18	62	105
Age at baseline in first trial (year)					
N	12	13	18	62	105
Mean (SD)	3.1 ( 1.7)	9.6 ( 1.6)	14.8 ( 1.4)	36.5 ( 11.9)	25.7 ( 16.3)
Median	3.0	10.0	15.0	34.5	23.0
Min ; Max	1 ; 6	7 ; 12	13 ; 17	18 ; 65	1 ; 65
Country, N (%)					
N	12 (100.0)	13 (100.0)	18 (100.0)	62 (100.0)	105 (100.0)
Canada	1 ( 8.3)	3 ( 23.1)	-	-	4 ( 3.8)
France	-	-	-	2 ( 3.2)	2 ( 1.9)
Germany	1 ( 8.3)	-	1 ( 5.6)	3 ( 4.8)	5 ( 4.8)
Italy	1 ( 8.3)	-	1 ( 5.6)	2 ( 3.2)	4 ( 3.8)
Japan	1 ( 8.3)	2 ( 15.4)	-	8 ( 12.9)	11 ( 10.5)
Macedonia	-	-	-	4 ( 6.5)	4 ( 3.8)
Malaysia	-	2 ( 15.4)	-	4 ( 6.5)	6 ( 5.7)
Netherlands	-	-	-	3 ( 4.8)	3 ( 2.9)
Romania	-	-	-	1 ( 1.6)	1 ( 1.0)
Russia	-	-	3 ( 16.7)	2 ( 3.2)	5 ( 4.8)
South Africa	-	-	-	4 ( 6.5)	4 ( 3.8)
Taiwan	2 ( 16.7)	-	-	1 ( 1.6)	3 ( 2.9)
Thailand	-	-	1 ( 5.6)	3 ( 4.8)	4 ( 3.8)
Turkey	-	-	2 ( 11.1)	2 ( 3.2)	4 ( 3.8)
United Kingdom	3 ( 25.0)	-	2 ( 11.1)	8 ( 12.9)	13 ( 12.4)
United States of America	3 ( 25.0)	6 ( 46.2)	8 ( 44.4)	15 ( 24.2)	32 ( 30.5)
Ethnicity, N (%)					
N	12 (100.0)	13 (100.0)	18 (100.0)	62 (100.0)	105 (100.0)
Hispanic or Latino	-	2 ( 15.4)	2 ( 11.1)	1 ( 1.6)	5 ( 4.8)
Not Hispanic or Latino	12 (100.0)	11 ( 84.6)	16 ( 88.9)	61 ( 98.4)	100 ( 95.2)
Race, N (%)					
N	12 (100.0)	13 (100.0)	18 (100.0)	62 (100.0)	105 (100.0)
White	8 ( 66.7)	5 ( 38.5)	15 ( 83.3)	37 ( 59.7)	65 ( 61.9)
Black	-	1 ( 7.7)	-	6 ( 9.7)	7 ( 6.7)
Asian	4 ( 33.3)	4 ( 30.8)	1 ( 5.6)	16 ( 25.8)	25 ( 23.8)
Other	-	3 ( 23.1)	2 ( 11.1)	3 ( 4.8)	8 ( 7.6)

Patients in 3775 are not included as their baseline information is as in the first trial, i.e. either 3747 or 3773.

From Trial 3773, only patients not previously treated in 3747 are included.

Source: BLA 125611/0 Module 2.7.3 Summary of Clinical Efficacy Table 3-2 page 39/80

The limited sample size in Blacks and Hispanics makes it challenging to reach conclusions about the efficacy of REBINYN in these races. Since the predilection for clinical bleeding is primarily dependent on the degree of Factor IX deficiency, race-related differences in efficacy of REBINYN are expected to be minimal. Therefore, it is reasonable to extrapolate the efficacy data from Whites and Asians to other ethnic groups.

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B is a recessive X-linked congenital bleeding disorder, caused by mutations in the FIX gene. It is the second most common coagulation factor deficiency. Most FIX deficiency occurs in males (86%) as expected for an X-linked disease, but females

comprise 3% of affected persons. More than 50% of all patients with hemophilia B have no known family history of the disease, and these are called sporadic cases. Deficiency or absence of FIX, results in impaired hemostasis, prolonged bleeding and rebleeding.

Hemophilia B is often characterized as severe, moderate or mild based on factor level correlating with the disease pattern. Subjects with FIX activity level <1% of normal are called severe, and have bleeds with no identified trauma, at least monthly, most frequently in joints. A FIX activity level of 1-5% is designated as moderate. These subjects have bleeds associated with mild trauma, and their bleeding frequency is less often than severe subjects. Subjects with mild deficiency FIX activity levels of ≥5-40% will have prolonged bleeding with worse than mild trauma as well as with surgery and since females are almost exclusively in this group, with menstruation.

A goal of modern hemophilia management is to prevent spontaneous bleeds, by supplying replacement factor that will maintain FIX activity levels to a value of >1-5%, i.e., in the range of subjects with the moderate form of the disease. This approach is known as routine prophylaxis.

The most serious complication of replacement therapy is inhibitor development. FIX inhibitors are allogenic antibodies to FIX that reduce or eliminate the activity of FIX. The magnitude of the inhibitor response can be quantified through the performance of a functional inhibitor assay from which a Bethesda unit (BU) inhibitor titer can be reported. The definitions are ≥0.6-5 BU for a 'low responding inhibitor' and ≥ 5 BU for a 'high responding inhibitor'.

Approximately 1–3% of patients with hemophilia B develops inhibitors following exposure to FIX. Among patients with severe hemophilia B the percentage has, however, been reported to be as high as 9%.

## 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Treatments for hemophilia B require replacement with FIX. FIX formulations include human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. FIX products, either plasma derived or recombinant, are commercially available. Recombinant factor IX (rFIX) preparations are the mainstay of therapy. Bypassing agents are available in the instance of inhibitor formation but these are not first-line therapy.

The currently approved products for FIX replacement are shown in the table below.

Table 2: Approved FIX products

Product	Category	Half-life (hr)	Year approved
Alphanine SD	Plasma derived	21	1990
Mononine	Plasma derived	23-31	1992
Benefix	Recombinant	18	1997
Rixubis	Recombinant	26.7	2013
Alprolix	Recombinant fusion protein	86.5	2014
Ixinity	Recombinant	17-31	2015
Idelvion	Recombinant, Albumin Fusion	104	2016

	Protein		
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All approved products are approved for the indications, control and prevention of bleeding episodes, and perioperative management. Rixubis, Alprolix, and Idelvion are approved for the additional indication of routine prophylaxis. The goal of maintaining FIX activity levels of at least 1% (routine prophylaxis) requires regularly scheduled FIX infusions. For routine prophylaxis, the labeled dosing frequency is twice a week for Rixubis, once every 7 to 10 days for Alprolix, and once every 7 days for Idelvion.

### 2.3 Safety and Efficacy of Pharmacologically Related Products

The safety issues that are identified in all of the Warnings Sections of the currently approved FIX replacement products include: inhibitor formation, anaphylaxis, thrombosis and nephrotic syndrome. For the plasma derived products (Alphanine SD and Mononine) there are additional Warnings of infection from viruses, Creutzfeldt-Jakob Syndrome, and disseminated intravascular coagulation. There do not appear to be any apparent difference in efficacy among the available products in terms of stopping or preventing bleeding, or for management of hemostasis in a perioperative context, when FIX products are given at doses and schedules that provide equal plasma FIX activities.

### 2.4 Previous Human Experience with the Product (Including Foreign Experience)

Human subjects were exposed for the first time to this product under the current IND 14008. Foreign experience data was not submitted with this IND. This product is approved in Europe and under review in Canada.

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

The evidence for safety and effectiveness for this product was collected under IND 14008. Key interactions were held with the FDA throughout the development process which included:

An End of Phase 2 meeting in October 2010 was held which included CMC agreements and clinical advice. FDA noted that to support a routine prophylaxis indication, reduction in the annualized bleeding rate (ABR) by 60% compared to on-demand treatment would be needed to be considered clinically significant. The clinical advice included that routine prophylaxis would reduce the annualized bleeding rate (ABR) by at least 60% from on-demand treatment. For the safety co-primary endpoint, the trial design should be based on ruling out more than one subject forming an inhibitor in 50 subjects who have 50 exposure days to the product, at the 95% confidence level. FDA encouraged the applicant to consider each subject serving as his/her own control. Written responses were sent for the Pre-BLA questions submitted. The key issues included the need for an Advisory Committee (AC). FDA stated that the need for the AC would be decided upon after receipt of the BLA. FDA also stated that the "routine prophylaxis" indication may be blocked by exclusivity by Rixubis.

REBINYN was given orphan designation for the "routine prophylaxis" indication in 2012. In a pre-BLA meeting in April 2015, we stated that the "routine prophylaxis" indication may be blocked by exclusivity by Rixubis.

### 2.6 Other Relevant Background Information

N/A

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

The submission was sufficiently organized to allow a complete clinical review without unreasonable difficulty. The submission consisted of five modules in the Common Technical Document Structure.

#### 3.2 Compliance with Good Clinical Practices and Submission Integrity

CBER Bioresearch Monitoring issued inspection assignments for four study sites under Protocol 3747. The sponsor reported that 40 clinical sites screened subjects under Protocol NN7999-3747 and of those, 39 enrolled individuals for participation in the study. The study was conducted at 39 clinical sites in 13 countries.

Table 3: BIMO Inspection Sites

Study Site #	Site Name	Location	Form FDA 483 Issued?	Final Inspection Classification
104	Mount Sinai Hospital	New York, NY	No	NAI
106	Children's Hospitals and Clinics of Minnesota	Minneapolis, MN	No	NAI
114	St. Michael's Medical Center	Newark, NJ	No	NAI
116	Gulf States Hemophilia & Thrombophilia Center	Houston, TX	No	NAI

NAI = No Action Indicated

The four sites were selected for inspection based on number of subjects enrolled at the sites. No significant regulatory violations were noted and a Form FDA 483 was not issued at any site. All for inspections were classified as NAI. Please refer to the BIMO review memo for full details.

#### 3.3 Financial Disclosures

Complete financial disclosures were provided for the studies and reviewed. No significant financial interests or conflicts were identified that could potentially bias the conduct of the study.

### 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

#### 4.1 Chemistry, Manufacturing, and Controls

REBINYN is a recombinant human factor IX with a 40 kDa polyethylene glycol (40 kDa PEG) moiety covalently attached to the N-linked glycans in the activation peptide. The molecular mass of nonacog beta pegol is approximately 98 kDa. When injected, nonacog beta pegol is activated by factor XIa or factor VIIa at the site of an injury. Once activated, REBINYN has the same structure as native activated factor IX.

The manufacturing process has been developed with few changes during the clinical development. The changes have resulted in virus safety, overall yield and in a higher purity with regard to product and process-related impurities. Comparability studies have shown that the REBINYN drug substance manufactured during non-clinical, phase 1, phase 3 and Process Performance Qualification batch manufacturing are of comparable quality. In-process controls (process parameters and in-process tests) have been established for each manufacturing step. Process parameters are controlled within defined ranges.

#### 4.2 Assay Validation

Required validation of applicable methods and release specifications have been completed. Please refer to the CMC review memo for complete details.

#### 4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology review memo for complete details.

The nonclinical program for N9-GP was comprised of multiple activity and safety studies to include: safety pharmacology, local tolerance, single- and repeat-dose toxicity studies. The animals studies included rats and cynomolgus monkeys. The majority of animals evaluated in the toxicity studies remained healthy until their scheduled sacrifice time point and had no overt signs of toxicity (e.g., irregularities in heart rate, body weight, food consumption, etc.). Any irregularities observed were transient, related to the species of the animal, or related to the development of cross-reacting neutralizing antibodies. These irregularities were not related to the 40 kDa PEG-rFIX. However, the exception to this was monkeys administered 3750 IU/kg/week for four weeks. Six out of eight monkeys in this dose level group exhibited mild but transient tremors. The cause of these tremors was unknown. Upon microscopic examination five monkeys in the high dose level group had substantial sub-meningeal congestion /hemorrhage in the brain and acute inflammatory cell infiltration in the spinal cord and hemorrhage associated with cellulitis in the skin/subcutis. The hemorrhage observed in these animals was most likely related to the development of cross-reacting neutralizing antibodies, resulting in acquired hemophilia. This is based on the prolongation of aPTT times in most animals, confirmation of neutralizing antibodies during the recovery period, and the clinical and pathological signs associated with a bleeding tendency (i.e., signs of bruising and/or swelling and hemorrhage).

The most notable observations in the histology of the animals in the toxicity studies were the accumulation of PEG in the choroid plexus and vacuolation in the choroid plexus and other organs. Vacuolation did not appear to be time- or dose-dependent, and the majority of the observed vacuolation was minimal or slight. Furthermore, vacuolation did not appear to cause any adverse structural effects to the cells, affect the metabolism of 40 kDa PEG-rFIX, or result in adverse clinical effects, neurological or otherwise. Accumulation of PEG in the connective tissue and cytoplasm of epithelial cells in the choroid plexus, and in blood within brain blood vessels was one of the most consistent observations in the histology. This observation was irrespective of the dose level of 40 kDa PEG-rFIX. Although PEG accumulation was observed in the Rowett nude rat studies, no clinical abnormalities were detected. There were no neurological deficits noted in the monkeys that were administered 350 or 1300 IU/kg/week for four weeks, even though PEG accumulation was observed in these animals. Currently, there is no clinical biomarker to assess choroid plexus function. However, the finding of PEG accumulation in the choroid plexus in nonclinical studies raises concern as to the

potential safety of 40 kDa PEG-rFIX in humans with respect to neurocognitive adverse events with chronic (long-term) use, especially in the pediatric and geriatric populations.

#### 4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology review memo for complete details.

The clinical pharmacology program comprised of four studies that evaluated the pharmacokinetic (PK) parameters of N9-GP.

##### 4.4.1 Mechanism of Action

Patients with hemophilia B are deficient in coagulation factor IX, which is required for effective hemostasis. Treatment with REBINYN temporarily replaces the missing clotting factor IX.

The PEGylation group in REBINYN is attached to specific N-linked glycans in the activation peptide of recombinant factor IX. Upon activation of REBINYN, the activation peptide including the 40 kilodalton polyethylene-glycol is cleaved off, leaving the native factor IX molecule, and generates activated factor IX similar to native factor IXa.

##### 4.4.2 Human Pharmacodynamics (PD)

The administration of REBINYN increases plasma levels of factor IX and can temporarily correct the coagulation defect in hemophilia B patients, as reflected by a decrease in aPTT. Pharmacodynamic response to FIX replacement is monitored via measurement of plasma FIX activity for clinical management and dosing of FIX products.

##### 4.4.3 Human Pharmacokinetics (PK)

PK samples were collected prior to dosing and at multiple time points up to 168 hours after dosing. The analysis of plasma samples was conducted using the one-stage clotting assay.

The PK of N9-GP was linear over a dose range of 25-100U/kg. The mean incremental recovery (IR) (measured at 30 minutes) of N9-GP was 0.0133 (U/mL)/(U/kg). Compared to rFIX, the IR of N9-GP was 94% higher and compared to pdFIX, the IR of N9-GP was 20% higher. The mean half-life of N9-GP was 93 hours. This was 5-fold longer compared to the subject's previous FIX products (rFIX and pdFIX). However, the half-life of N9-GP should be interpreted with caution because reported half-life of 93 hours of N9-GP is based on blood sampling of 168 hours. The mean clearance of N9-GP was 0.70 mL/h per kg, which was 10-fold slower compared to the subjects' previous FIX products (rFIX and pdFIX). The mean volume of distribution of N9-GP was 94.2 mL/kg. This was 43% lower compared to the subjects' previous FIX products (rFIX and pdFIX) indicating more N9-GP in systemic circulation than previous FIX products (rFIX and pdFIX).

#### 4.5 Statistical

Please refer to the Statistical Review Memo for complete details.

The statistical reviewer verified the primary and secondary endpoint analyses conducted by the Applicant in support of this BLA. The rate of inhibitory antibodies was reported and a 1-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. Estimates of the annualized bleeding rates for each dose were provided with 95% Confidence Intervals (Cis). The first test for ABR aimed to establish that the 40 IU/kg leads to a bleeding frequency below 4.8 bleeding episodes

per year by evaluating whether the upper confidence limit for the annualized bleeding rate is below 4.8. PRO data was summarized and listed using descriptive statistics. The treatment duration was included as an offset covariate in the Poisson analysis model for routine prophylaxis, which incorporates the subjects who withdraw prior to 52 weeks of treatment.

No major statistical issues were identified during the review of this BLA.

#### 4.6 Pharmacovigilance

A CDER Pharmacovigilance Consult was obtained to provide safety information to determine if vacuolization was reported in patients using pegylated products. Their team noted the adverse events theoretically associated with vacuolization are nonspecific and common, therefore cannot be causally linked.

The analyses of the preclinical data raised a concern for the potential safety of REBINYN in the long-term use in pediatric and elderly populations. A postmarketing study or REMS (Risk Evaluation and Mitigation Strategies) is not necessary for this product with approval for the following indications: on-demand treatment and control of bleeding, and perioperative management of bleeding, as no safety risk associated with the study drug was observed in the clinical trials for these indications.

The product will be under routine pharmacovigilance, and if concerns arise from surveillance activities, or from further clinical studies, the risk management strategy can be amended to address a newly identified concern.

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

#### 5.1 Review Strategy

The review of this original BLA was based on the clinical data from four clinical studies provided in BLA 125611/0.

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

Documents pertinent to this review were provided in 125611/0 and IND 14008, including the clinical summary, overview, and clinical study reports (Sections 2.5, 2.7, 5.3.5.).

#### 5.3 Table of Studies/Clinical Trials

Table 4: Clinical Trials:

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
<i>Previously treated patients with haemophilia B</i>						
Safety and 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.	<i>First human dose trial</i> A Multi-Centre, Multi-National, Open-Label, Dose Escalation Trial Evaluating Safety and Pharmacokinetics of Ascending Intravenous Doses of 40K Pegylated Recombinant FX in Non-Bleeding Patients with Haemophilia B.	Single dose

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	<i>Prophylaxis:</i> 10 IU/kg or 40 IU/kg once weekly.  <i>Treatment of bleeding episodes:</i> 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes).  <i>Pharmacokinetics:</i> 10 or 40 IU/kg single dose and steady-state.  i.v.	<i>Pivotal trial</i> 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
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	<i>Pre-operative loading dose:</i> 80 IU/kg  <i>Post-operative dose(s):</i> 40 IU/kg	<i>Surgery trial</i> 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
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.	<i>Prophylaxis:</i> 40 IU/kg once weekly.  <i>Treatment of bleeding episodes:</i> 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes).  i.v.	<i>Paediatric trial</i> 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
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	<i>Prophylaxis:</i> 10 IU/kg or 40 IU/kg once weekly.  <i>Treatment of bleeding episodes:</i> 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes).	<i>Extension trial</i> 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
<i>Previously untreated patients with haemophilia B</i>						
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.	<i>Prophylaxis:</i> 40 IU/kg once weekly.  <i>Treatment of bleeding episodes:</i> 40 IU/kg (mild/moderate bleeding episodes); 80 IU/kg (severe bleeding episodes).	<i>Trial in previously untreated patients</i> 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

Source: BLA 125611/0 Module 5.2 Tabular Listing of all Clinical Studies p2-5



#### 5.4 Consultations

A consultation from the Division of Cardiovascular and Renal Products at the Center for Drug Evaluation and Research was obtained on March 2, 2017. The nonclinical studies reported accumulation of PEG and vacuolation in renal tissue. The clinical trials did not find any safety signal that was clearly likely to be caused by PEG accumulation. However, it is unclear whether the clinical monitoring of renal function was adequate to detect all clinically important renal signs or symptoms. Therefore, the following renal consult questions were asked:

- Are there any additional clinical concerns related to nephrotoxicity based on potential PEG vacuole formation or PEG accumulation in cortical tubules?
- Please provide a discussion of potential renal risks of chronic administration in elderly and pediatric patients.
- Please comment on the adequacy of the renal monitoring parameters, frequency and sample size that were performed in the Phase 3 study in the context of making a comprehensive assessment of risks to the renal system from REBINYN.
- Please provide a discussion of the extent of feasible clinical monitoring (either in the context of the ongoing studies or future studies) if any, that should be considered to make a comprehensive assessment of risks to the renal system from REBINYN.

The renal consultant stated that similar vacuoles have been seen in preclinical and clinical studies of other PEG products with a clinical signal for acute or chronic nephrotoxicity to date and there was no signal for acute or chronic nephrotoxicity based on the available data with REBINYN. The renal consult noted that the clinical database was small and limited to younger subjects with preserved renal function and nephrotoxicity would be more evident in a population at a higher risk. The consult concluded that monitoring of renal function was generally adequate and would not recommend additional clinical monitoring. The consult stated that there are no significant clinical concerns related to nephrotoxicity.

A CDER Pharmacovigilance Consult was obtained to determine if vacuolization was reported in patients using pegylated products. CDER's pharmacovigilance team stated that three products (Pegasys, Cimzia, and Macugen) are the only products that contain the larger form (i.e., 40 kDa) of PEG and they are chronically used, therefore may offer better safety data on long term PEG accumulation. The lack of specificity for adverse events associated with vacuolization limits the utility of FAERS data. The adverse events theoretically associated with vacuolization are nonspecific and common, therefore cannot be causally linked.

##### 5.4.1 Advisory Committee Meeting

OTAT management along with the Chair of this BLA made the decision for discussion of this product at the Advisory Committee. The Blood Product Advisory Committee was held on April 4<sup>th</sup>, 2017. This meeting was held to seek advice regarding the preclinical findings of PEG accumulation in the choroid plexus. Of interest was the Committee's assessment regarding safety in the intended population, particularly in the pediatric and elderly populations, and in the setting of chronic administration. FDA asked whether monitoring, specifically of neurologic function, should be provided for the safety of the intended patient population. In addition, FDA asked whether additional data are necessary to evaluate the issue of PEG accumulation in the choroid plexus.

The Committee provided the following recommendations:

- 1) No issues with short-term use of REBINYN (perioperative and on-demand treatment)
- 2) A standardized approach was needed for neurocognitive assessments to be collected and done postmarketing
- 3) Additional preclinical testing may be warranted but could be done post approval
- 4) For routine prophylaxis, the AC was concerned about the pediatric population (less than 2 years of age) and the geriatric population, but commented that no arbitrary age cutoff should be used.

#### 5.4.2 External Consults/Collaborations

No external consultations were conducted.

#### 5.5 Literature Reviewed (if applicable)

Montgomery RR, Gill JC, Scott JP. Hemophilia and von Willebrand's Disease (2003). In: Nathan and Oski's Hematology of Infancy and Childhood, 6th, Nathan DG, Orkin SH, Ginsberg D, Look AT (Eds), WB Saunders, Philadelphia.

Guidelines for the Management of Hemophilia (2005). *World Federation of Hemophilia*, [www.wfh.org](http://www.wfh.org).

Bullinger, M., Globe, D., Wasserman, J., Young, N.L., & von Mackensen, S. (2009). Challenges of Patient-Reported Outcome Assessment in Hemophilia care- a State of the Art Review. *Value In Health*, 12(5), 808-820.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1: NN7999-3747

A multicenter, single-blind trial evaluating safety and efficacy, including pharmacokinetics of REBINYN when used for treatment and prophylaxis of bleeding episodes in subjects with hemophilia B.

Clinical Trials Identifier: NCT01333111

Initiated: April 29, 2011 Trial Completed: April 2, 2013

#### 6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to evaluate the immunogenicity.

The secondary objectives included:

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

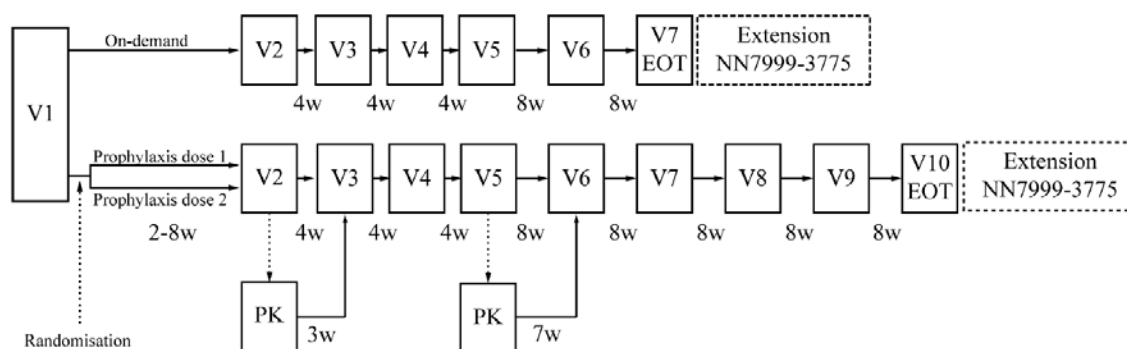
#### 6.1.2 Design Overview

This was a multinational, multi-center, randomized, single-blind trial. Single-blind in this trial meant that subjects on prophylaxis did not know whether they were randomized to

the low dose (10 U/kg) or the high dose (40 U/kg) REBINYN. This information was also concealed from the investigator; however, the investigator had the possibility to measure FIX activity levels during the trial. The investigator could potentially be unblinded during the trial.

A minimum of 60 subjects were to complete the trial. The trial had two prophylaxis arms (one low dose [10 U/kg] and one high dose [40 U/kg]) and one on-demand arm. Each subject in a prophylaxis arm was to attain 50 exposure days (EDs) to REBINYN throughout the trial. 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). Once the clinical investigator decided to randomize subjects to receive routine prophylaxis, randomization to one of the two prophylaxis arms was done at Visit 2, as shown below.

Figure 1: Trial 3747 Design Overview



Source: BLA125611/0 CSR 3747 Figure9-1 page 46/1237

The duration of the trial for each subject in the prophylaxis arms was planned for 52 weeks, and for subjects in the on-demand arm it was 28 weeks.

The clinical efficacy assessments for treatment of bleeding episodes were based on the treatment of all bleeding episodes in the 28-week on-demand arm and the two prophylaxis arms, using a standard 4-point scale of "excellent, good, moderate or poor response". See definitions of this scale below in Section 6.1.8.

### 6.1.3 Population

A total of 68 subjects were planned for enrollment. Subjects were males with hemophilia B in the age range of 13–70 years.

The following were the key inclusion criteria:

1. Male subjects with moderately severe or severe congenital hemophilia B with a FIX activity  $\leq 2\%$  according to medical records
2. History of at least 150 exposure days to other FIX products
3. Subjects 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 subjects currently on prophylaxis

The following were the key exclusion criteria:

1. Known or suspected hypersensitivity to trial product or related products
2. Known history of FIX inhibitors based on existing medical records, laboratory report reviews and patient and LAR interviews

3. Current FIX inhibitors  $\geq 0.6$  BU (central laboratory)
4. HIV positive with a viral load  $\geq 400,000$  copies/mL and/or CD4+ lymphocyte count  $\leq 200/\mu\text{L}$
5. Previous arterial thrombotic events (e.g. myocardial infarction and intracranial thrombosis) or previous deep venous thrombosis or pulmonary embolism (as defined by available medical records)
6. Platelet count  $< 50,000$  platelets/ $\mu\text{L}$  at screening (local laboratory)
7. ALT  $> 3$  times the upper limit of normal reference ranges at screening (central laboratory)
8. Creatinine level  $\geq 1.5$  times above upper normal limit at screening (central laboratory)
9. Immune modulating or chemotherapeutic medication

*Reviewer Comment: The inclusion and exclusion criteria are acceptable.*

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

The following investigational medicinal product was used in the trial: REBINYN  
REBINYN was presented as freeze-dried powder in single-use vials with a nominal content of 500 U/vial or 2000 U/vial. Both strengths were to be reconstituted with 4.2 mL of histidine solvent for IV injection. Histidine solvent (4.2 mL/vial) was provided together with REBINYN. All investigational medicinal products were supplied by Novo Nordisk A/S, Denmark.

Subjects enrolled in a prophylaxis arm received either 10 U/kg (low dose arm) or 40 U/kg (high dose arm) REBINYN doses once weekly (every 7th day  $\pm$  24 hours), depending on which prophylaxis arm they were randomized. For all subjects in the trial, the dose levels of REBINYN for treatment of a mild or moderate bleeding episode were a single dose of 40 U/kg. A severe bleeding episode was to be treated immediately at home or at a local emergency room with 80 U/kg.

#### 6.1.5 Directions for Use

Subjects enrolled in a prophylaxis arm received either 10 U/kg (low dose arm) or 40 U/kg (high dose arm) REBINYN doses once weekly (every 7th day  $\pm$  24 hours), depending on which prophylaxis arm they were randomized. REBINYN was supplied as freeze-dried powder in single-use vials with a nominal content of 2000 U/vial to be reconstituted with 4.2 mL of histidine solvent for IV injection.

#### 6.1.6 Sites and Centers

The trial was conducted at 39 sites in 13 countries.

Figure 2: Trial Sites

Country	Number of sites that screened patients	Number of sites that enrolled patients
France	1	1
Germany	3	3
Italy	2	2
Japan	6	5
Macedonia	2	2
Malaysia	1	1
Netherlands	1	1
Russia	2	2
South Africa	1	1
Thailand	2	2
Turkey	3	3
United Kingdom	4	4
United States	12	12
<b>Total</b>	<b>40</b>	<b>39</b>

Source: BLA125611/0 CSR 3747 Table6-1 page 36/1237

### 6.1.7 Surveillance/Monitoring

Please see below for the monitoring for those on prophylaxis:

Table 5: Trial 3747 Monitoring

Visit number	Screening	Prophylaxis period <sup>1</sup> (PK evaluation was performed at Visit 2 and Visit 5 for a subgroup of patients)									Follow up visit <sup>5</sup> FU	Inhibitor follow up visits <sup>6</sup> IFU1-3
		2 <sup>2,20</sup>	3	4	5 <sup>2</sup>	6	7	8	9	10/ end-of-trial <sup>4</sup>		
Weeks in relation to Visit 2	Not later than 2 wks prior to Visit 2	0	4 wks	8 wks	12 wks	20 wks	28 wks	36 wks	44 wks	52 wks	4 wks after Visit 10/end-of-trial visit	Every 4 wks after end-of-trial visit
Visit Window	2-8 wks prior to Visit 2	-	±1w	±1w	±1w	±2w	±2w	±2w	±2w	±2w	±2w	±1w
<b>PATIENT RELATED INFORMATION</b>												
Informed consent	X											
Inclusion / Exclusion criteria	X	X <sup>7</sup>										
Withdrawal criteria		X	X	X	X	X	X	X	X	X		
Randomisation		X										
Patient Reported Outcomes <sup>8</sup>	X									X		
Demography	X											
Concomitant illness	X											
Medical history incl. Haemophilia treatment history	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Date & time of last coagulation factor administration	X	X	X	X	X	X	X	X	X	X	X	
Bleeding episodes including Diary compliance review	X <sup>9</sup>	X <sup>9</sup>	X	X	X	X	X	X	X	X	X	
<b>ADVERSE EVENTS<sup>10</sup></b>												
Adverse Events <sup>11</sup>	X	X	X	X	X	X	X	X	X	X	X	X
<b>CLINICAL ASSESSMENTS<sup>10</sup></b>												
Body measurements	X	X <sup>11</sup>			X <sup>11</sup>					X <sup>11</sup>		
Physical examination	X	X					X			X	X	

	Screening	Prophylaxis period <sup>1</sup> (PK evaluation was performed at Visit 2 and Visit 5 for a subgroup of patients)										Follow up visit <sup>5</sup>	Inhibitor follow up visits <sup>6</sup>
Visit number	1	2 <sup>2,20</sup>	3	4	5 <sup>2</sup>	6	7	8	9	10/ end-of-trial <sup>1</sup>	FU	IFU1-3	
Weeks in relation to Visit 2	Not later than 2 wks prior to Visit 2	0	4 wks	8 wks	12 wks	20 wks	28 wks	36 wks	44 wks	52 wks	4 wks after Visit 10/end-of-trial visit	Every 4 wks after end-of-trial visit	
Visit Window	2-8 wks prior to Visit 2	-	±1w	±1w	±1w	±2w	±2w	±2w	±2w	±2w	±2w	±1w	
Vital signs	X										X		
- pre-dose	X	X			X					X			
- post-dose (30 min)	X	X											
ECG	X												
Injection site inspection													
- pre-dose		X											
- post-dose (30 min)		X											
<b>LOCAL LABORATORY ASSESSMENTS<sup>7</sup></b>													
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis <sup>13</sup>	X	X										X	
<b>CENTRAL LABORATORY ASSESSMENTS<sup>7</sup></b>													
Biochemistry	X	X	X	X	X	X	X	X	X	X	X		
Coagulation related parameters	X												
- pre-dose		X <sup>14</sup>	X	X	X <sup>14</sup>	X	X	X	X	X	X		
- post-dose (30 min)		X	X	X	X <sup>14</sup>	X	X	X	X	X	X		
FIX activity	X										X	X	
-pre-dose		X <sup>14</sup>	X	X	X <sup>14</sup>	X	X	X	X	X	X		
-post-dose (30 min)		X	X	X	X <sup>14</sup>	X	X	X	X	X	X		
<b>NONACOG BETA PEGOL ADMINISTRATION</b>													
Adm. of nonacog beta pegol	X <sup>17</sup> X	X	X	X	X	X	X	X	X	X			
Nonacog beta pegol dispensing for home treatment	X	X	X	X	X	X	X	X	X	X			
Nonacog beta pegol accountability	X	X	X	X	X	X	X	X	X	X			
<b>TRAINING AND REMINDERS</b>													
Trial Card Dispensing	X												
Home treatment and Diary training		X	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>	X <sup>18</sup>			
<b>PROPHYLAXIS PERIOD<sup>1</sup></b>													
Visit number	1	2 <sup>2,20</sup>	3	4	5 <sup>2</sup>	6	7	8	9	10/ end-of-trial <sup>1</sup>	FU	IFU1-3	
Weeks in relation to Visit 2	Not later than 2 wks prior to Visit 2	0	4 wks	8 wks	12 wks	20 wks	28 wks	36 wks	44 wks	52 wks	4 wks after Visit 10/end-of-trial visit	Every 4 wks after end-of-trial visit	
Visit Window	2-8 wks prior to Visit 2	-	±1w	±1w	±1w	±2w	±2w	±2w	±2w	±2w	±2w	±1w	
Diary dispensing		X											
Telephone contact to patients (halfway through the home-treatment period)		X	X	X	X	X	X	X	X	X			
IV/IVRS	X	X	X	X	X	X	X	X	X	X			
End of trial <sup>1</sup>										X	X	X	

The severity of bleeding episodes was defined as:  
Mild/Moderate: Bleeding episodes that were uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal- or subcutaneous bleeds. These bleeding episodes could be treated at home and details of the bleeding episodes were entered in the electronic diary by the subject.

Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeds were categorized as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the hemoglobin level (>3g/dl) were also to be reported as severe. These bleeding episodes had to be treated immediately or at the local emergency room, and the trial personnel had to be contacted. The details of severe bleeding episodes had to be entered in the electronic case report form (eCRF) by the investigator or trial personnel. Traumatic bleedings at other locations than described above could always be considered severe at the discretion of the investigator.

*Reviewer Comment:*

*A complete neurological physical exam (PE) was performed at the initial assessment. The eCRFs show a full initial PE and then only documents another PE if anything has changed from the previous exam based on the examiner asking the subject a review of systems. In this case, where the safety of the product remains in question, as a detailed history and exam was not performed, it is unclear to know the thoroughness of the neurological exam that was performed at each site and whether a subtle change would have been noted, since it was not documented. If a subject does not volunteer to report a neurologic symptom (or may not know they are experiencing a symptom), a physical exam would not be performed where a neurologic finding may be present. A thorough exam would have provided more data and may have alleviated the doubt of this missing information in making a clear assessment of the neurologic/neurocognitive findings. Detecting neurologic safety findings from the PEG in the animal data may require a detailed neurologic and neurocognitive assessments.*

#### 6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was the incidence of inhibitory antibodies against FIX, defined as titer  $\geq 0.6$  BU.

Secondary confirmatory efficacy endpoints were the hemostatic effect of REBINYN when used 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; number of bleeding episodes per subject during routine prophylaxis.

The four-point scale was based on the improvement in signs of bleeding; additionally, pain relief, swelling and range of motion at the bleeding site was taken into account. The evaluation using the four-point scale reflected the hemostatic response from the time of treatment until 8 hours following treatment. The Four Point Scale utilized is below.

#### Four Point Scale

- 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 8 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 or worsening of symptoms within 8 hours after two injections

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

The full analysis and safety analysis set comprised of all dosed subjects. Although the two analysis sets were identical, safety analyses were performed on the safety analysis set, whereas efficacy and PK analyses were performed on the full analysis set.

### 6.1.10 Study Population and Disposition

There were 168 protocol deviations at the subject level.

Table 6: Protocol Deviations

Deviation	Number of deviations
Inclusion/exclusion criteria	7
Informed consent	12
Laboratory issues/laboratory samples	34
Assessment deviations	12
Treatment compliance	55
Trial product handling/trial product issues	18
Visit window	1
Other/miscellaneous issues	29
<i>Total</i>	<i>168</i>

Source: BLA125611/0 CSR 3747 Table10-17page 120/1237

A total of 7 of the recorded important deviations were related to violation of the selection criteria. These deviations were mostly related to subjects being included before historical data or laboratory reports were available for assessment of the eligibility criteria. However, all the subjects were eligible once the historical data and laboratory reports were received and reviewed.

#### 6.1.10.1 Populations Enrolled/Analyzed

This trial enrolled hemophilia B subjects aged 13–70 years.

##### 6.1.10.1.1 Demographics

The trial consisted of males with hemophilia B and median age of 30 years. The majority was White (64.9%) and the second largest group was Asian (21.6%). The median age was lower in the 40 IU/kg arm as compared to the 10 IU/kg arm (26 years v. 32.5 years, respectively).

Table 7: Demographics

	10 IU/kg	40IU/kg	Both	On-demand	Total
Number of Subjects	30	29	59	15	74
Age at baseline(years) Mean (SD)	32.4 (13.9)	30.0(15.8)	31.2 (14.8)	32.4 (12.0)	31.4 (14.2)
Median	32.5	26.0	30.0	33.0	30.0
Min;Max	14;56	13;65	13;65	13;51	13;65
United States (%)	5 (16.7)	6 (20.7)	11 (18.6)	10 (66.7)	21 (28.4)
Ethnicity					
Hispanic or Latino (%)	2 (6.7)	-	2 (3.4)	-	2 (2.7)



Race (%)					
Asian	8 (26.7)	5 (17.2)	13 (22)	3 (20)	16 (21.6)
Black	2 (6.7)	3 (10.3)	5 (8.5)	-	5 (6.8)
White	16 (53.3)	21 (72.4)	37 (62.7)	11 (73.3)	48 (64.9)
Other	4 (13.3)	-	4 (6.8)	1 (6.7)	5 (6.8)

Source: Adapted from BLA125611/0 CSR 3747 Table10-2 page 113/1237

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects were male with congenital hemophilia B with a FIX activity of  $\leq 2\%$ . All previously-treated-patients (PTPs) had a history of 150 exposure days (EDs) to other FIX products and no history of inhibitors.

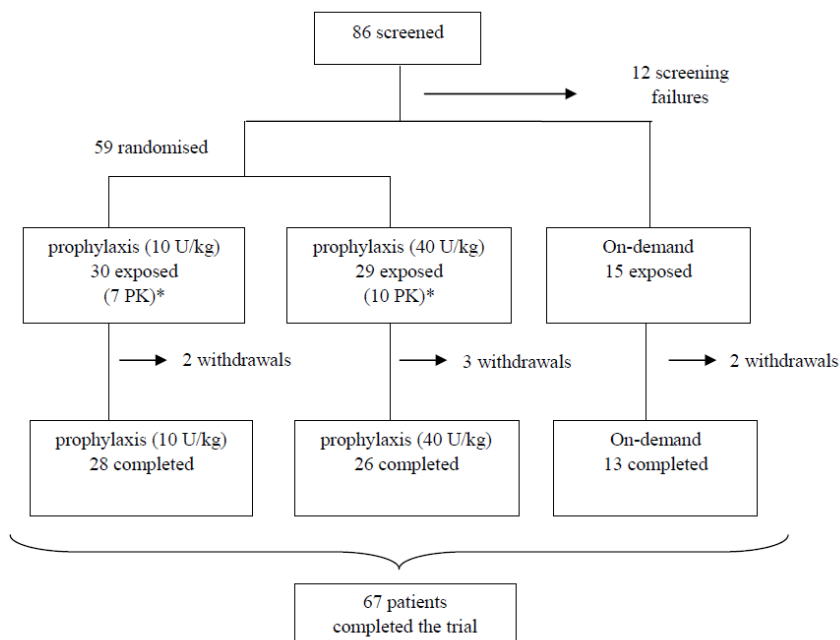
Before trial entry, 52.7% subjects received prophylactic treatments with either recombinant or plasma derived FIX products. The remainder received on demand treatment. Of those previously on prophylaxis, 37 subjects had a mean of 6.9 bleeding episodes in the past year that required treatment. Forty out of the 74 subjects had a target joint (i.e. 3 or more spontaneous bleeds have had occurred in a 6-month period in the same joint). Of those receiving on-demand therapy, all 35 subjects required at least one treatment for a bleeding episode in the 12 months (mean number of bleeds was 20.8) preceding study entry.

*Reviewer Comment: The bleeding history of those on prophylaxis versus on demand is as expected. Fourteen subjects with moderate hemophilia were included in this trial. An information request was sent to the applicant on February 3, 2017 requesting to conduct a sensitivity analysis for ABR (overall, spontaneous, traumatic) excluding the moderate hemophilia B subjects. The ABR was found to be comparable. Please refer to statistical review memo for complete analysis.*

#### 6.1.10.1.3 Subject Disposition

A total of 86 subjects were screened for this trial and 74 were enrolled, of which 18 were adolescents (13-17 years), and 67 completed the trial. Randomization was performed between the two prophylaxis arms. A total of 17 subjects were enrolled for PK assessments and 16 completed the assessments.

Figure 3: Subject Disposition



Source: BLA125611/0 CSR 3747 Figure10-1 page 111/1237

## 6.1.11 Efficacy Analyses

### 6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was the incidence of inhibitor rate. Please also refer to the Safety Analyses below for further details. No inhibitors were detected.

### 6.1.11.2 Analyses of Secondary Endpoints

There was a total of 345 bleeds in 55 subjects. The majority of the bleeds were spontaneous (225/65.8%), 114 bleeds (33.6%) were traumatic bleeds and 0.6% were due to minor surgery. The most frequent location of bleeds was in a joint (78.5%). The bleeds were classified as mild/moderate in 99.7% of the cases and one bleed was classified as severe. Five of a total of 345 bleeds had re-bleeds. There were more traumatic bleeds among adolescents compared with adults. In adolescents, bleeds in the 40IU/kg arm had a shorter duration and shorter time from first dose of REBINYN to stop the bleed compared to the 10IU/kg arm, whereas the reverse was seen in adults.

Table 8: Details of Bleeds

	10 IU/kg	40 IU/kg	Both	On-demand	Total
Number of subjects with bleeds	25	16	41	14	55
Number of bleeds	<b>132</b>	<b>70</b>	202	143	345
Cause of bleed (%)					
Spontaneous	91 (68.9)	<b>34 (48.6)</b>	125 (61.9)	102 (71.3)	227 (65.8)
Traumatic	39 (29.5)	36 (51.4)	75 (37.1)	41 (28.7)	116 (33.6)
Other	2 (1.6)	-	2 (1)	-	2 (0.6)
Site of Bleed, N (%)	122 (100)	69 (100)	191 (100)	140 (100)	331 (100)
Joint	99 (81.1)	54 (78.3)	153 (80.1)	107 (76.4)	260 (78.5)
Classification of bleed					

Mild/Moderate	131 (99.2)	70 (100)	201 (99.5)	143 (100)	344 (99.7)
Severe	1 (0.8)	-	1 (0.5)	-	1 (0.3)
Time since last dose N, (%)	119 (100)	66 (100)	185 (100)	134 (100)	319 (100)
≤4 days	71 (59.7)	32 (48.5)	103 (55.7)	10 (7.5)	113 (35.4)
≥ 4 days	48 (40.3)	34 (51.5)	82 (44.3)	124 (92.5)	206 (64.6)

Source: Adapted from BLA125611/0 CSR 3747 Table11-1 page 124/1237

A total of 202 bleeds were treated in the prophylaxis arm. More bleeds occurred in the 10 IU/kg arm compared with the 40 IU/kg arm due to a higher number of spontaneous bleeds in the 10 IU/kg arm. Approximately half (48.6%) of the bleeds in the 40IU/kg group were spontaneous bleeds, despite reaching FVIII trough levels of 40%. More than half (56%) of the spontaneous bleeds involved a target joint in the 40IU/kg group.

A total of three subjects without target joints at baseline had three or more bleeds in the same joint during the trial. The 40 IU/kg prophylaxis arm had the lowest proportion of bleeds involving a target joint.

The hemostatic response after treatment of a bleed with REBINYN was evaluated on a four point scale, as described above. Of the 345 bleeding episodes, 341 bleeds were rated. The success rate for all bleeds was 92.4% (95% CI: 87.0; 95.6), which was above the pre-specified success rate of 80%. (Non-inferiority (to 80%) was to be concluded if the lower 95% confidence limit for the success rate was above 65%.) The success rate was higher for the 40 IU/kg arm and higher for adolescents. The success rate was lower for spontaneous bleeds compared with traumatic bleeds and higher for subjects who prior to the trial were on on-demand treatment compared with those on prophylaxis. The majority of bleeds received REBINYN within two hours from the start of the bleed.

In the on-demand group, the majority of bleeds were treated by one injection (87.4%). In the 40 IU/kg and 10 IU/kg prophylaxis groups, 98.5% and 92.9% of the bleeding episodes were resolved with only one injection of REBINYN, respectively. Furthermore, the highest number of injections to treat a bleed in the 40 IU/kg arm was three injections, compared to 9 injections in the 10 IU/kg prophylaxis arm and 6 injections in the on-demand arm.

*Reviewer Comment: There study results are limited in that only one major/severe bleeding episode was evaluated. The dose for treatment of major bleeding is higher than the dose for the treatment of minor bleeding. Therefore, the efficacy data in minor bleeding cannot be extrapolated to support the efficacy of the dose for the treatment of major bleeding. The data to support the indication for the treatment of major bleeds was extrapolated from the data in subjects who underwent major surgical procedures, as the perioperative dose of 80 IU/kg is the same as the proposed dose for the treatment of major bleeding.*

Table 9: Hemostatic Response and Success Rate- Full Analysis Set

	10 IU/kg	40 IU/kg	Both	On-demand	Total
Number of subjects with bleeds (%)	25 (83.3)	16 (55.2)	41 (69.5)	14 (93.3)	55 (74.3)
Hemostatic Response, N (%)	132 (100)	70 (100)	202 (100)	143 (100)	345 (100)
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)

Source: Adapted from BLA125611/0 CSR 3747 Table11-3 page 127/1237

*Reviewer Comment: The applicant also analyzed bleeds with missing outcomes as treatment failures. This resulted in a success rate of 91.3% and also supported the results of the original analysis.*

The number of bleeding episodes per subject during routine prophylaxis was assessed using the individual annualized bleeding rate. The estimated annualized bleeding rate was 4.56 (95% CI: 3.01; 6.90) in the 10 U/kg arm and 2.51 (95% CI: 1.42; 4.43) in the 40IU/kg arm. The median annualized bleeding rate was 2.93 (IQR: 0.99; 6.02) in the 10IU/kg arm and 1.04 (IQR: 0.00; 4.00).

Table 10: Annualized Bleeding Rate

	10 IU/kg	40 IU/kg	Both
ABR (N)	30	29	59
Median [IQR]	2.93 [0.99;6.02]	<b>1.04 [0.0;4.0]</b>	2.04 [0.0;5.0]
Poisson Estimate of ABR (95% CI)	4.56 (3.01;6.90)	2.51 (1.42;4.43)	3.55 (2.53; 4.98)

Source: Adapted from BLA125611/0 CSR 3747 Table11-5 page 129/1237

There was no statistical difference between the two prophylaxis arms. The median [Interquartile Range; IQR] ABR for the On-Demand group was 15.58 [9.61; 20.29].

*Reviewer Comment: The applicant's statistical analysis used an estimate of the ABR for subjects on demand as 12 bleeding episodes per year. An ABR less than 4.8 was statistically significant if the upper bound of the two-sided 95% confidence interval was below 4.8. This was not a mean or median ABR, but an absolute value. Therefore, prophylaxis with 40 U/kg was considered efficacious, whereas efficacy of 10 U/kg was not demonstrated. Also, although subjects achieved 40% trough levels, the third quartile IQR was four. This means that for the number of subjects who experienced bleeding over the median, the frequency of bleeding was similar to other long acting products. Of note, direct comparison between products should be interpreted with caution. Thus, the clinical benefit of the trough levels of 40% at 5.4 days, following the study drug administration in 29 subjects did not substantially impact the risk of spontaneous bleeding. The reasons for this observation are unclear. This clinical reviewer estimates that this IQR would be expected to be lower, especially if the subjects were achieving trough levels up to 40%. This confirms there was ongoing bleeding in these subjects, despite high trough levels.*

For spontaneous bleeds, the bleeding rate was lower in the 40 IU/kg arm compared with the 10 U/kg arm. For traumatic bleeds, the bleeding rates were similar in the two prophylaxis arms. See Table 11, below. The median [IQR] Spontaneous Bleeds ABR and Traumatic Bleeds for the On-Demand group was 11.12 [7.16;15.81] and 1.73 [0.00;8.95], respective

Table 11: Spontaneous and Traumatic Bleeds

Dose (N)	10 IU/kg (30)	40 IU/kg (29)	Both (59)
Spontaneous bleeds	91	34	125
ABR Median [IQR]	3.14 [1.78;5.56]	1.22 [0.48;3.10]	2.20 [1.35;3.57]
Poisson Estimate of ABR (95% CI)	0.97 (0.00;4.01)	0.00 (0.00;0.98)	0.00 (0.00; 2.08)
Traumatic bleeds	39	36	75
ABR Median [IQR]	1.35 [0.81;2.24]	1.29 [0.76;2.19]	1.32 [0.92;1.90]
Poisson Estimate of ABR (95% CI)	0.98 (0.00;1.93)	0.00 (0.00;2.04)	0.00 (0.00; 1.98)

Source: Adapted from BLA125611/0 CSR 3747 Table11-7 page 133/1237

*Reviewer Comment: As previously stated, approximately half (48.6%) of the bleeds in the 40IU/kg group were spontaneous bleeds, despite reaching FVIII trough levels of 40%. In general, subjects with mild hemophilia (with 40% FVIII activity levels), should experience little to no spontaneous bleeds. Thus, the higher levels of trough levels of FVIII activity (40%) levels observed as compared to other available long acting products did not result in a reduction in spontaneous bleeding rates. The ABR of both spontaneous and traumatic bleeds are within the expected range as noted with other long acting products. The ABR for the on-demand group were as expected, and comparable to other long acting products (there has been no head to head comparison, and direct comparison should be done with caution in any of the conclusions above.*

For those subjects who were on prophylaxis prior to the trial, a decrease from the historical bleeding rate to the actual bleeding rate during the trial was observed for both prophylaxis arms (10 IU/kg: 5.13 to 4.68 bleeds/patient/year and 40 IU/kg: 7.49 to 3.33 bleeds/patient/year). There was also a marked decrease from the historical bleeding rate to the bleeding rate during the trial for subjects who were on demand treatment prior to the trial (10 IU/kg: 17.9 to 4.3 bleeds/patient/year and 40 IU/kg: 21.2 to 1.32 bleeds/patient/year).

The dose level to be used for treatment of a mild or moderate bleeding episode was 40 IU/kg, while the dose level to be used for treatment of a severe bleeding episode was 80U/kg. There was 1 severe bleeding episode in the trial (in the 10 IU/kg prophylaxis arm); all other bleeds were mild or moderate.

PK: PK assessments were performed with the one stage clotting assay. The FIX levels declined exponentially with time for both dose assessments. All individual PK values for 10 IU/kg were below any value of the individual values for 40 IU/kg. AUC and FIX trough levels was 3–4 fold higher in the 40 IU/kg arm compared with the 10 U/kg arm, while no differences were observed for incremental recovery. The t<sub>1/2</sub> for single-dose was 93 hours in the 10 IU/kg arm and 85 hours in the 40 IU/kg arm, while at steady-state t<sub>1/2</sub> was 107 hours in the 10 IU/kg arm and 111 hours in the 40 IU/kg arm. Clearance was however similar between groups, and indicates no differences in elimination between the 10 U/kg and 40 U/kg groups.

*Reviewer Comment: After a single dose of 10 IU/kg and 40 IU/kg, the subject's mean trough levels were 5% and 17%, respectively. Steady state (at 5.4 days) trough levels had a max of 43%. For those subjects in the 40 IU/kg, steady state mean trough levels were 31%. The ABR for the 40 IU/kg and 10IU/kg groups is not lower compared to other FIX products, as these two dose levels achieved high trough levels which should*

*maintain hemostasis. Subject phenotype could contribute to these differences in the ABR*

#### 6.1.11.3 Subpopulation Analyses

There were 18 adolescents included in this trial. Seven subjects treated with 10 IU/kg and nine subjects treated with 40 IU/kg of the study drug. Two subjects were treated with on-demand treatment. The median [IQR] ABR for subjects in the 10 IU/kg cohort and 40 IU/kg cohort was 2.08 [0;5.84] and 1.93 [0;4], respectively.

*Reviewer Comment: These ABR's are comparable to the overall data. The overall median ABR for adolescents was 2.0, which is similar to the median ABR for adults alone (2.04).*

#### 6.1.11.4 Dropouts and/or Discontinuations

Subjects could withdraw at any time. A subject had to withdraw if one of the following criteria applied:

- Development of FIX inhibitors ( $\geq 0.6$  BU) at two consecutive tests at the central laboratory
- Anaphylaxis to trial product
- Significant thromboembolic event
- Incapacity or unwillingness to follow the trial procedures

A total of 7 subjects were withdrawn but not due to adverse events. Reasons for withdrawal included non-compliance, subject's decision, and subjects undergoing major surgery, unwilling to follow trial procedure, personal reasons, and ineffective therapy, these subjects were included in the efficacy analysis until the time of withdrawal.

#### 6.1.11.5 Exploratory and Post Hoc Analyses

Patient reported outcomes (PRO) data were collected to assess change in health related, disease and age-specific quality of life and treatment satisfaction from the screening visit to end-of-trial visit. This data was received from the HAEMO-QOL questionnaire and European quality of life index was given to both adult and adolescent subjects in this trial. An improvement in the European Questionnaire was observed in the 40 IU/kg group. The change in quality of life was substantial in the adult population.

*Reviewer Comment: The PROs used in this trial need to be validated before these can be used to inform the prescriber. The statistical analyses of these endpoints were not pre-specified, therefore, these endpoints will not be included in the label.*

#### 6.1.12 Safety Analyses

A total of 74 subjects were exposed to REBINYN. All evaluations of safety were based on the safety analysis set, including all 74 dosed subjects thus being equal to the full analysis set. In the two prophylaxis arms, the mean prophylactic doses were 10.5 and 42.2 IU/kg.

##### 6.1.12.1 Methods

All adverse events either observed by the investigator or reported by the subjects had to be recorded by the investigator and evaluated. In addition, the subjects were to be asked during each contact with the trial site if they had had any adverse events (including any changes in concomitant illness or new illnesses) since the last visit.

#### 6.1.12.2 Overview of Adverse Events

In general, there were no apparent differences in the safety-related results among the treatment arms or between the age groups (adolescents and adults).

The primary endpoint was incidence of inhibitors against FIX defined as titer  $\geq 0.6$  BU. No inhibitors were detected and the 1-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 6%, thus the primary test succeeded as the upper confidence limit was below 10.7%. As the Nijmegen modified FIX Bethesda assay was compromised by high residual FIX activity, a (b) (4) Nijmegen modified FIX Bethesda assay was developed). In this assay, the residual FIX activity in the samples used for inhibitor testing was reduced through (b) (4). No inhibitors were detected using the (b) (4) Nijmegen modified FIX Bethesda assay.

*Reviewer Comment: Please refer to the CMC memo for the details of the quality of this heat/cold assay.*

There were 3 subjects who developed Anti-REBINYN (FIX + PEG) binding antibodies. One subject, 30 years old, was transiently positive for these antibodies after 31 exposure days (EDs). The second subject, 14 years old, was also transiently positive before exposure to REBINYN and again positive after 5 EDs. The third subject, 23 years old, was transiently positive before exposure to REBINYN and again positive after 21 EDs. There was no inhibitory effect in any of the 3 subjects.

*Reviewer Comment: The binding antibodies were transient and had no inhibitory effect. Thus, clinically significant findings were not observed despite this observation.*

There was one subject who developed Anti-HCP (host cell protein) antibodies prior to exposure of study drug. There were no associated adverse events.

*Reviewer Comment: This is not a safety issue, since the subject was challenged with the product and had no other associated adverse reaction.*

A total of 215 adverse events were reported for 60 (81.1%) subjects exposed to REBINYN corresponding to a rate of 3.33 adverse events per patient years of exposure. The vast majority (97%) of the adverse events was of mild or moderate severity and also the main part (91%) were judged by the investigator to be unlikely related to REBINYN. The most commonly reported adverse events were nasopharyngitis (13 events in 10 subjects [13.5%]), influenza (10 events in 8 subjects [10.8%]) and upper respiratory tract infection (10 events in 8 subjects [10.8%]).

None of the adverse events led to the withdrawal of subjects. No thromboembolic events were reported and no allergic reactions related to REBINYN were reported.

A total of 19 adverse events in 12 subjects (16.2%) were judged to be possibly or probably related to REBINYN by the investigator. All of the adverse events were non serious and of mild severity.

There were seven adverse events that were severe. None of the severe adverse events were judged to be related to REBINYN by the investigator. Furthermore, two of the severe adverse events (hip fracture and skin ulcer) were also serious and 2 (skin ulcer and age-related macular degeneration) were not resolved at the end of the trial.

Reviewer Comment: This clinical reviewer judged these as not related to the study drug.

Table 12: Adverse Events with Probable Relation

Patient number	Age (Years)	Regimen	ED <sup>a</sup>	Preferred term	Relationship	Serious	Severity	Outcome
(b) (6)	15	On-demand	1	Speech disorder developmental (largiloquent [i.e., excessive talking])	Possible	No	Mild	Recovered
			2	Speech disorder developmental (largiloquent [i.e., excessive talking])	Possible	No	Mild	Recovered
	16	Prophylaxis 40 U/kg	3	Overdose	Probable	No	Mild	Recovered
			9	Incorrect dose administered	Probable	No	Mild	Recovered
	51	Prophylaxis 40 U/kg	51	Pain in extremity	Possible	No	Mild	Not recovered
	54	Prophylaxis 40 U/kg	1	Fatigue	Possible	No	Mild	Recovered
			8	Ear pruritus	Possible	No	Mild	Recovered
			8	Headache	Possible	No	Mild	Recovered
	45	Prophylaxis 10 U/kg	1	Fatigue	Possible	No	Mild	Recovered
			1	Headache	Possible	No	Mild	Recovered
			1	Laryngeal pain	Possible	No	Mild	Recovered
	26	Prophylaxis 10 U/kg	6	Hot flush	Possible	No	Mild	Recovered
			6	White blood cell count increased	Possible	No	Mild	Recovered
	30	Prophylaxis 40 U/kg	14	Overdose	Probable	No	Mild	Recovered
	24	Prophylaxis 10 U/kg	32	Accidental overdose	Probable	No	Mild	Recovered
	51	Prophylaxis 10 U/kg	1	Incorrect dose administered	Probable	No	Mild	Recovered
	44	On-demand	1	Nausea	Possible	No	Mild	Recovered
	36	Prophylaxis 40 U/kg	4	Palpitations	Possible	No	Mild	Recovered
	52	Prophylaxis 10 U/kg	6	Fatigue	Possible	No	Mild	Not recovered

a: ED is the number of exposure days before onset of event

Source: BLA125611/0 CSR 3747 Table12-3 page 151/1237

Reviewer Comment: This clinical reviewer judged the following as possibly related to the study drug including: fatigue, headache, and nausea.

### 6.1.12.3 Deaths

No deaths were reported.

### 6.1.12.4 Nonfatal Serious Adverse Events

A total of 4 of the adverse events were serious and none of these were judged to be related to REBINYN.

Table 13: Serious Adverse Events

Patient number	Age (Years)	Regimen	ED <sup>a</sup>	Preferred term	Relationship	Severity	Outcome
(b) (6)	45	Prophylaxis 40 U/kg	19	Hip fracture	Unlikely	Severe	Recovered
	65	Prophylaxis 40 U/kg	17	Skin ulcer	Unlikely	Severe	Not recovered
	15	Prophylaxis 10 U/kg	7	Retroperitoneal haematoma	Unlikely	Moderate	Recovered
	14	Prophylaxis 40 U/kg	4	Abdominal pain	Unlikely	Mild	Recovered

According to the protocol (Appendix 16.1.1) the retroperitoneal haematoma in patient 703001 should have been reported as a severe bleeding episode.

a: ED is the number of exposure days before onset of event

Source: BLA125611/0 CSR 3747 Table12-5 page 155/1237

Reviewer Comment: This clinical reviewer judged these as not related to the study drug

### 6.1.12.5 Adverse Events of Special Interest (AESI)

Few events were related to dosing (incorrect dose administered [2 events in 2 subjects], medication error [2 events in 1 subject], overdose [2 events in 2 subjects] and accidental



overdose [1 event]). Out of these, 4 events were also reported as medical events of special interest.

*Reviewer Comment: The four events of special interest occurred in a 16 year old, 30 year old, 24 year old, and 51 year old. They all involved one overdose of the study drug and had no adverse event post the overdose. All subjects recovered. The numbers of events (dosing and medication errors) are of low frequency and in this clinical reviewer's opinion does not warrant inclusion of this information in the label.*

#### 6.1.12.6 Clinical Laboratory Test Results

The following included the clinically relevant changes in laboratory tests:

These included 4 events of increased CRP in 4 subjects (5.4%), 4 events of increased F1+2 level in 2 subjects (2.7%), 1 event of increased blood creatine phosphokinase in 1 subject (1.4%), 1 event of increased blood fibrinogen in 1 subject (1.4%), 1 event of decreased hemoglobin in 1 subject (1.4%), 1 event of abnormal F1+2 level in 1 subject (1.4%), 1 event of prolonged PT in 1 subject (1.4%) and 1 event of increased white blood cell count in 1 subject (1.4%). In addition, 3 events of eosinophilia in 3 subjects (4.1%) and 1 event of anemia in 1 subject (1.4%) were reported. All events were judged to be unlikely related to REBINYN, except the event of increased white blood cell count, which was judged to be possibly related to REBINYN by the investigator. None of the events were serious or severe.

On urinalysis testing, three subjects tested positive for glucose at one time point; two of these subjects were positive only before dosing. The third subject was positive at the End of Treatment (EOT) visit. There were 27 subjects who tested positive for proteinuria; 12 tested positive prior to dosing with the study drug. There were 15 subjects who had positive test results for protein after dosing with REBINYN. Seven subjects had one positive test (1 at an intermediate visit and 6 at EOT). Six subjects had two positive tests (3 at baseline and EOT, 2 at an intermediate visit and EOT, 1 at baseline and an intermediate visit). One subject had three positive tests. One subject had 4 positive tests (all four visits).

*Reviewer Comment: This clinical reviewer judges all these events as unlikely related to the study drug. A renal consult was obtained on March 2, 2017, due to the preclinical studies reporting accumulation of PEG and vacuolation in renal tissue. The renal consult notes that the clinical database was small and limited to younger subjects with preserved renal function and nephrotoxicity would be more evident in a population at a higher risk. The consult concluded that monitoring of renal function was generally adequate and would not recommend additional clinical monitoring. The consult stated that there are no significant clinical concerns related to nephrotoxicity. Thus, based on these recommendations the clinical reviewer does not recommend additional pre-marketing studies to evaluate for nephrotoxicity related to PEG.*

*Although not specified by the Applicant as Adverse Events of Interest, the clinical reviewer also focused on any neurologic/cognitive findings in the clinical studies given the finding in the preclinical data. No significant neuro/cognitive issues were identified in the clinical studies.*

#### 6.1.12.7 Dropouts and/or Discontinuations

Seven subjects were withdrawn due to ineffective therapy: two for non-compliance, two subjects withdrew as they were undergoing major surgery, one met withdrawal criteria, one was the subject's decision, and one was reported as personal reasons. There was no withdrawal due to an AE.

#### 6.1.13 Study Summary and Conclusions

The primary endpoint was incidence of inhibitory antibodies against FIX defined as titer  $\geq 0.6$  BU. No inhibitory antibodies were detected.

The secondary objectives included the evaluation of hemostasis and ABRs. The success rate for treatment of all bleeds was 92.4% (95% CI: 87.0; 95.6) and the hemostatic effect of REBINYN was confirmed statistically. The estimated annualized bleeding rate was 4.56 (95% CI: 3.01; 6.90) in the 10 U/kg arm and 2.51 (95% CI: 1.42; 4.43) in the 40 U/kg arm. The median annualized bleeding rate was 2.93 (IQR: 0.99; 6.02) in the 10 U/kg arm and 1.04 (IQR: 0.00; 4.00) in the 40 U/kg arm. REBINYN administered once weekly maintained FIX activity significantly above 0.01 U/mL and the estimated mean FIX trough levels during the trial were 0.085 U/mL for the 10 U/kg arm and 0.273 U/mL for the 40 U/kg arm. Of the total 202 bleeds in the prophylaxis arms, 132 bleeds (65.3%) occurred in the 10 U/kg arm and 70 bleeds (34.7%) occurred in the 40 U/kg arm. The majority were spontaneous (61.9%), most occurred in a joint (80.1%) and the vast majority were mild/moderate (99.5%). In the 40 IU/kg arm, 10 out of 15 (66.7%) subjects with target joints at baseline did not bleed in a target joint during the trial. In the 10 U/kg arm, this number was 1 out of 13 (7.7%) subjects. The proportion of bleeds that were resolved with 1 injection of REBINYN was 87.0% for all bleeds, 84.1% for bleeds in the 10 U/kg arm, 98.6% for bleeds in the 40 U/kg arm and 83.9% for bleeds in the on-demand arm.

A total of 215 adverse events were reported in 60 (81.1%) subjects exposed to REBINYN. The most commonly reported adverse events were nasopharyngitis (13 events in 10 subjects [13.5%]), influenza (10 events in 8 subjects [10.8%]) and upper respiratory tract infection (10 events in 8 subjects [10.8%]). In all, 19 adverse events in 12 subjects (16.2%) were judged to be possibly or probably related to REBINYN by the investigator. All the related adverse events were non-serious and mild of severity. A total of 4 serious adverse events (hip fracture, skin ulcer, retroperitoneal hematoma and abdominal pain) were reported in 4 subjects (5.4%), corresponding to a rate of 0.06 serious adverse events per patient years of exposure, and none of these were judged to be related to REBINYN. No subjects were withdrawn due to adverse events.

One subject was positive for anti-HCP antibodies before and after exposure to REBINYN. No thromboembolic events and no allergic reactions related to REBINYN occurred during the trial. Results of safety laboratory parameters and other safety-related examinations did not indicate clinically relevant changes as a result of REBINYN treatment.

*Reviewer Comment: There are no issues with the efficacy of this product for on demand treatment and routine prophylaxis in adult and adolescents. No clear safety signal from accumulation of PEGylation was observed in the clinical trials. However, it is unclear whether the monitoring of neurologic function was adequate to detect all clinically important neurologic signs or symptoms and therefore, chronic use of this product would not be recommended with this uncertainty. Short term/acute use (on demand treatment)*

*is unlikely to lead to accumulation of PEG or vacuolation in the choroid plexus as the unfavorable effects are more likely with long-term exposure. This reviewer acknowledges that the data to support on demand bleeding treatment of acute bleeding (and perioperative management) of bleeding is limited. However, based on the risk/benefit profile including the duration of exposure and total dose necessary in this indication, it is reasonable to assume that the safety profile favors marketing approval of REBINYN. This is also consistent with the opinion of the majority of the members of the AC.*

## 6.2 Trial #2: Trial NN7999-3773

An open-label, multi-center, uncontrolled trial to assess efficacy and safety of REBINYN during surgical procedures in subjects with hemophilia B

Clinical Trials Identifier: NCT01386528

Initiated: June 8, 2012 Trial Completed: December 2, 2013

### 6.2.1 Objectives

The primary objective was to evaluate the hemostatic effect of REBINYN during surgical procedures in subjects with Hemophilia B.

The secondary objectives were to evaluate the general safety, including immunogenicity, when used for prevention and treatment of bleeding throughout the surgical period; to evaluate the hemostatic effect of REBINYN during the postoperative period.

### 6.2.2 Design Overview

This was an open label multicenter uncontrolled trial evaluating efficacy and safety of REBINYN in surgical procedures in subjects with Hemophilia B.

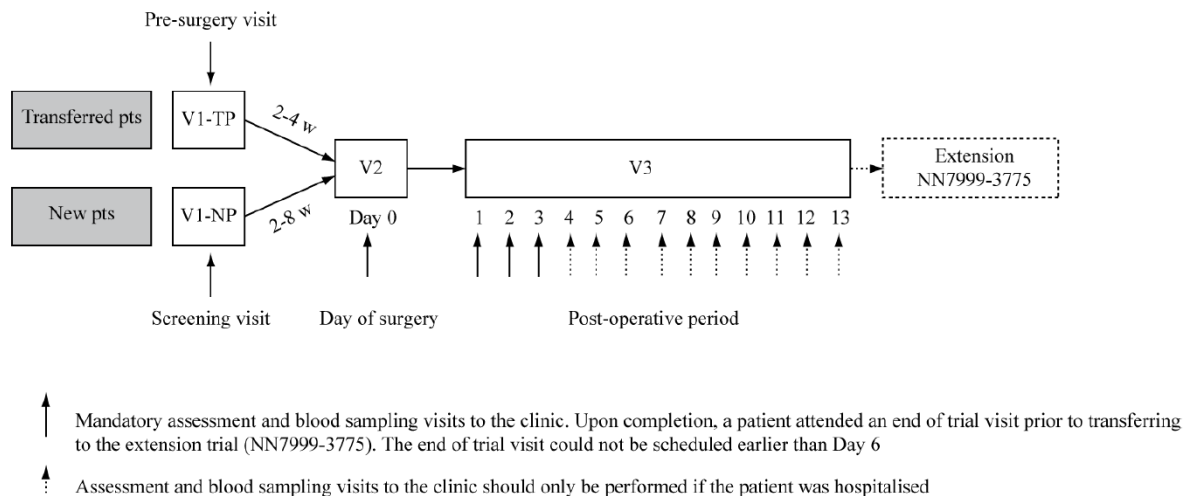
Subjects enrolled could be recruited from the pivotal trial or the extension trial. In addition, new subjects could also be recruited into the present trial. After the trial, subjects were offered to continue on prophylaxis or on-demand treatment in the extension trial. The total duration was estimated to be between 3-12 weeks. Daily assessments were conducted until Day 3. Efficacy was assessed using a 4 point scale of "excellent, good, moderate, or poor." This is described below:

Clinical evaluation of hemostatic response during surgery was assessed immediately after surgery (last stitch) by the surgeon, anesthesiologist and/or investigator based on experience as follows:

1. Excellent: Better than expected/predicted in this type of procedure.
2. Good: As expected in this type of procedure.
3. Moderate: Less than optimal for the type of procedure but hemostatic response maintained without change of treatment regimen.
4. Poor: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required.

Transfusion requirements, hemoglobin, consumption and number of doses per procedure were recorded.

Figure 4: Design Overview



V1-TP is the pre-surgery visit for patients transferred from the pivotal trial (NN7999-3747) or the extension trial (NN7999-3775)

V1-NP is the screening visit for new patients.

After completion of the surgery trial, patients could continue into the extension trial (NN7999-3775)

Source: BLA125611/0 CSR 3773 Figure 9-1 page 27/364

### 6.2.3 Population

The trial enrolled Hemophilia B subjects between 13 and 70 years. A total of 10 surgeries in 5-10 subjects were planned to be completed in the trial. The following were the inclusion criteria:

1. Written informed consent from the patient or the child's parent/LAR obtained before any trial related activities. Trial-related activities were any procedure that would not have been performed during normal management of the patient.
2. Male patients with moderately severe or severe congenital hemophilia B with a FIX activity <2% according to medical records.
3. History of at least 150 exposure days to other FIX products.
4. Age 13-70 years (both inclusive)
5. Body Mass Index (BMI)  $\leq 35$ .
6. Scheduled major surgery.

The following were the key exclusion criteria:

1. Known or suspected hypersensitivity to trial products or related products.
2. Known history of FIX inhibitors based on available medical record, laboratory report reviews and patient and patient's LAR interviews.
3. Current FIX inhibitors  $\geq 0.6$  BU (central laboratory).
4. HIV positive, with viral load  $\geq 400,000$  copies/mL and/or CD4+ lymphocyte count  $\leq 200/\mu\text{L}$ .
5. Previous arterial thrombotic events (e.g. myocardial infarction and intracranial thrombosis) or previous deep venous thrombosis or pulmonary embolism (as defined by available medical records).
6. Platelet count < 50,000 platelets/ $\mu\text{L}$  at screening.
7. ALT > 3 times the upper limit of normal reference ranges at screening.
8. Creatinine level  $\geq 1.5$  times above upper normal limit at screening.
9. Immune modulating or chemotherapeutic medication.

10. Any disease or condition (liver, kidney, inflammatory and mental disorders included) which, according to the investigator's judgment, could imply a potential hazard to the patient, interfere with the trial participation or trial outcome.

The subject could withdraw anytime. A subject was to be withdrawn if:

1. Development of FIX inhibitors  $\geq 0.6$  BU at two consecutive tests at the central lab.
2. Anaphylaxis to trial product.
3. Significant thromboembolic event prior to day of surgery.
4. Incapacity or unwillingness to follow the trial procedures.

The definition of major surgery submitted in the IND states:

Any invasive operative procedure that require several days of substitution therapy and/or where any one or more of the following occur:

- A body cavity is entered
- A mesenchymal barrier (e.g. pleura, peritoneum or dura) is crossed
- A fascial plane is opened
- An organ is removed
- Normal anatomy is operatively altered

Minor surgery is defined as:

Any invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated. Examples of minor surgery included implanting pumps in subcutaneous tissue, skin biopsies or simple dental procedures.

#### 6.2.4 Study Treatments or Agents Mandated by the Protocol

The subject was dosed once with 40 IU/kg of REBINYN. The FIX activity after 30 minutes was measured and used to determine if dose adjustments were necessary during the perioperative period.

All subjects received a preoperative dose of 80 IU/kg 15 minutes to 4 hours prior to the surgery and before any procedures. During the postoperative period a dose of 40 IU/kg was given, 24-48 hours after the preoperative dose. After Day 3, the study drug was dosed at the investigator's discretion according to measured or expected FIX activity.

#### 6.2.5 Directions for Use

REBINYN was supplied as freeze-dried powder in single-use vials with a nominal content of 2000 U/vial to be reconstituted with 4.2 mL of histidine solvent for IV injection.

#### 6.2.6 Sites and Centers

Of the 11 sites in nine countries that screened subjects, 10 sites in eight countries enrolled subjects. The 10 sites in eight countries that enrolled patients were: Italy (1 site), Malaysia (1 site), Romania (1 site), South Africa (1 site), Taiwan (1 site), Turkey (1 site), UK (2 sites), US (2 sites).

#### 6.2.7 Surveillance/Monitoring

The trial consisted of the following visits:

- Visit 1-New Patients:
  - Screening visit (2-8 weeks prior to the day of surgery)
  - Visit 1-Transferring Patients:
    - Pre-surgery visit for transferred patients (2-4 weeks prior to the day of surgery)
- Visit 2 (Day 0): Day of surgery

- Visit 3 (Day 1 - Day 13): Post-operative period
- End of trial visit
- Follow-up visit
- Inhibitor follow-up visit 1-3

#### 6.2.8 Endpoints and Criteria for Study Success

Surgical procedures and duration, hemostatic effect, consumption of REBINYN, transfusion requirements, and bleeding episodes were the assessments used in the criteria for study success.

#### 6.2.9 Statistical Considerations & Statistical Analysis Plan

There was no formal hypothesis testing. Endpoints were summarized and listed using descriptive statistics. No interim analysis was planned or performed.

#### 6.2.10 Study Population and Disposition

All were males with congenital hemophilia B with a FIX activity level  $\leq 2\%$ . All were previously-treated-patients (PTPs) with a history of at least 150 EDs to other FIX products and no history of inhibitors.

##### 6.2.10.1 Populations Enrolled/Analyzed

A total of 15 subjects were screened and 13 were dosed with REBINYN and completed the trial.

##### 6.2.10.1.1 Demographics

All subjects were male with Hemophilia B, with a median age of 39 years. There was only one pediatric subject, and was 15 years old. The majority were White (61.5%). There were 23.1% Asian and 15.4% Black subjects in the trial.

##### 6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Subjects met the criteria as described in Section 6.2.10. All were PTPs with a history of at least 150 EDs to other FIX products and no history of inhibitors.

Eleven subjects had severe hemophilia B (FIX activity  $< 1\%$ ) and 2 had moderate hemophilia B (FIX activity  $1\%-\leq 2\%$ ). Most of the subjects (76.9%) had received prophylactic treatment with either recombinant or plasma derived FIX products. The remainder followed an on-demand treatment regimen.

##### 6.2.10.1.3 Subject Disposition

Out of the 13 subjects, 6 were new to the REBINYN clinical development program, 2 were transferred from the adult study, and 5 were transferred from the extension trial. New subjects received 2 doses of 40 IU/kg of REBINYN to observe for hypersensitivity and anaphylactic reactions and to determine the 30 minutes post dose FIX activity level. The two doses were separated by 4-8 days.

For all subjects, the day of surgery was to be planned to allow for at least 7 days between the last dose in the pre-surgery period and the dose given at the day of surgery.

A total of 41 protocol deviations were reported in the trial. Five were reported at the trial site level and 36 were at the subject level. The trial site level deviations included those related to product handling, monitoring visits not performed according to the protocol, a

sub-investigator not being trained in the protocol prior to doing protocol related work, and material that was given to subjects without being submitted to the local ethics committee.

The 36 deviations were the following: 2 related to missing informed consent documents, 1 related to inclusion/exclusion criteria, 4 related to treatment compliance ( mismatch between dispensed and returned trial product), 14 due to assessment deviations (blood samples not drawn according to the protocol), 13 related to laboratory sample deviations (hemolyzed samples or samples that were drawn but not received by the lab), and 2 “other” related deviations where the staff forgot to give the subject an ID card stating he was participating in a trial, and a study nurse completing a subject diary while the subject was hospitalized.

*Reviewer Comment: These protocol deviations did not impact the interpretability of the results.*

### 6.2.11 Efficacy Analyses

A total of 13 surgeries were performed in 13 subjects.

#### 6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was hemostatic effect during surgery which was evaluated on a four point scale. The details of the surgeries in the context of hemostatic response are detailed below.

This clinical reviewer judged the following to be minor surgeries.

Table 14: Minor Surgeries

Surgery Location	Transfusion	Hemostatic Response
Oral Cavity	-	Excellent
Oral Cavity	-	Excellent
Mouth	-	Excellent
Rectum	-	Excellent

Source: Adapted from BLA125611/0 CSR 3773 Table 11-2 page 86/364

This clinical reviewer judged the following to be major surgeries.

Table 15: Major Surgeries

Surgery Location	Transfusion	Hemostatic Response
Left Knee	-	Excellent
Left Knee	-	Excellent
Bilateral Knee	-	Excellent
Right Knee	2x300mL	Good
Right Knee	-	Excellent
Right Hip	-	Excellent
Left Hip	3x250mL	Good
Right Achilles Tendon	-	Excellent
Right ankle	-	Good

Source: Adapted from BLA125611/0 CSR 3773 Table 11-2 page 86/364

The hemostatic effect was rated as “excellent” in 10 (76.9%) and as “good” in 3 (23.1%) of the surgeries by this clinical reviewer (see Section 6.2.2 for definition of hemostatic response ratings), which would have a success rate of 100%.

Two subjects were transfused, 7 had drainage volumes up to 2.5 L and 3 subjects had post-surgical wound hematomas. Three bleeding episodes occurred in 3 subjects (2 at the surgical site and 1 was traumatic).

*Reviewer Comment:*

*Upon review of the list of surgeries, nine are judged to be major and four are minor, by this clinical reviewer. Based on the definition in the protocol for minor procedures, the four surgeries judged to be minor were dental procedures and one was ablation of rectal warts. There were two major surgeries that required transfusions and yet were rated excellent and good. It is unclear when these ratings occurred. Both should have been rated as “good”, since these outcomes were as expected. The amount of drainage volume is acceptable for major orthopedic surgeries. Five subjects had additional doses in the post-surgery period (max 3 doses). Of note, although four surgeries were judged to be minor, these subjects were given 80 IU/kg preoperatively, as the applicant judged these to be major surgeries. If these subjects were dosed with 40 IU/kg, (the preoperative dose to be given in minor surgeries), the outcomes of the hemostatic response may have been different. Overall, the study resulted in a 100% success rate, as all the surgeries had either “good” or “excellent” hemostatic outcomes.*

#### 6.2.11.2 Analyses of Secondary Endpoints

The administration of REBINYN during surgery occurred preoperatively, peri- and postoperatively. The mean pre-operative dose was 81.8 IU/kg (80.9-83.6 IU/kg). These were administered as one single injection and none of the subjects needed additional doses on the day of surgery.

*Reviewer Comment: The recommended dose was 80 IU/kg and the mean is slightly higher, but the differences between the recommended dose and actual dose administered is small enough to permit reliable interpretation of the dose. .*

Two subjects required transfusions of 250-300 ml of packed red blood cells (PRBCs). One of these subjects had low hemoglobin values post-operatively and was not reported as clinically significant by the investigator or as an adverse event. The other subject, who also had low hemoglobin levels, was reported as an adverse event. The mean 1 hour post-surgery hemoglobin level was 8.37 mmol/L ranging from 7.08 to 9.43 mmol/L. The mean 24 hours post-surgery hemoglobin level was 7.99 mmol/L ranging from 5.77 to 9.50 mmol/L.

Postoperatively, 12 of the 13 subjects required REBINYN on post-surgery days 1-6. The mean number of doses was 2.2 ranging from 1-4 doses. The mean dose was 41.1U/kg ranging from 20-42.4 U/kg.

The 2 subjects who received transfusions were on post-surgery Days 1 and 2 (Subject 1) and Day 6 (Subject 2). The first subject received 250ml of PRBCs on Day 1 and 2. Subject 2 received 300 ml of PRBCs on Day 6. Seven of the 13 had post-surgical drainage volumes ranging from 2-2500 ml. Three subjects had post-surgical wound hematomas. None of the hematomas required evacuation.



The post-operative efficacy assessments for hemostatic efficacy took place between Days 1-13. Of the 12 subjects evaluable for post-operative hemostatic efficacy assessments, three achieved adequate hemostatic control within post-operative Days 1-6, and were therefore considered to have completed the trial. Of the remaining 9 subjects, who were monitored for hemostatic efficacy during post-operative Days 7-13, the mean number of doses was 1.7 ranging from 1-3 doses. The mean dose was 41.9 IU/kg ranging from 41.2 to 42.4 IU/kg. None of the subjects required transfusions during post-surgery Days 7-13. None of the subjects had drainage volume. Two subjects continued to have wound hematomas. One resolved after Day 7 and one remained until the end of the trial.

There were 3 post-operative bleeds reported in 3 subjects. Two occurred at the surgical site (post-operative day 1 and 3) and one was a traumatic bleed that occurred on post-operative day 6. All bleeds resolved with one injection of 40 IU/kg. The hemostatic response was rated according to the 4 point scale and rated good and excellent for the surgical site bleeds. The traumatic bleed response was rated as excellent.

The mean consumption per subject was 328 IU/kg/subject ranging from 165-543 IU/kg/subject.

*Reviewer Comment:*

*The overall consumption is appropriate. It is reassuring that no subject required any transfusions after post-operative day seven. For both subjects who bled post-operatively, these subjects should have been rated as good rather than excellent as these were expected results, based on the definition in the protocol. Since the traumatic bleed occurred without relation to the surgery, it is understood giving this an excellent rating.*

6.2.11.3 Subpopulation Analyses

N/A

6.2.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

6.2.12.2 Overview of Adverse Events

Of the 13 exposed subjects, 9 subjects had 16 adverse events. None of these were serious or severe. None of the events led to withdrawal. Two events in two subjects were evaluated to be related to the study drug by the investigator. One is detailed below as an adverse event of special interest in which the subject had pruritus. The other event was an increased serum ferritin which was judged as mild. The event was based on blood samples drawn at the end of the trial visit and reported as not recovered.

There were no thromboembolic events reported. No FIX inhibitors were reported. No anti REBINYN binding antibodies were detected. One subject had a positive Anti-HCP antibody. The antibody titer decreased over time; there were no associated clinical signs or symptoms associated with this finding.

All AEs reported are below.

Table 16: Adverse Events

	Total N (%)	E
Number of patients	13	
Total time in trial (years)	1.32	
Total number of exposure days	90	
All adverse events	9 ( 69.2)	16
Gastrointestinal disorders	3 ( 23.1)	4
Epigastric discomfort	1 ( 7.7)	1
Nausea	1 ( 7.7)	1
Oral mucosal erythema	1 ( 7.7)	1
Vomiting	1 ( 7.7)	1
General disorders and administration site conditions	2 ( 15.4)	2
Face oedema	1 ( 7.7)	1
Pyrexia	1 ( 7.7)	1
Injury, poisoning and procedural complications	2 ( 15.4)	2
Excoriation	1 ( 7.7)	1
Fall	1 ( 7.7)	1
Musculoskeletal and connective tissue disorders	2 ( 15.4)	2
Musculoskeletal discomfort	1 ( 7.7)	1
Pain in extremity	1 ( 7.7)	1
Vascular disorders	2 ( 15.4)	2
Haemorrhage	1 ( 7.7)	1
Hypertension	1 ( 7.7)	1
Blood and lymphatic system disorders	1 ( 7.7)	1
Anaemia	1 ( 7.7)	1
Eye disorders	1 ( 7.7)	1
Conjunctival haemorrhage	1 ( 7.7)	1
Investigations	1 ( 7.7)	1
Serum ferritin increased	1 ( 7.7)	1
Skin and subcutaneous tissue disorders	1 ( 7.7)	1
Pruritus	1 ( 7.7)	1

All adverse events in this table are treatment emergent.

N: Number of patients with adverse event, %: Percentage of patients with adverse event,

E: Number of adverse events

Source: BLA125611/0 CSR 3773 Table 12-2 page 95/364

### 6.2.12.3 Deaths

There were no deaths.

### 6.2.12.4 Nonfatal Serious Adverse Events

There were no SAEs.

#### 6.2.12.5 Adverse Events of Special Interest (AESI)

One AE was reported as an event of special interest. The subject reported pruritus and as this could be potentially allergy related. The event occurred after the first exposure as itching on the back and right ear for 10 minutes. No treatment was given. The event was of mild severity and the subject recovered from the event. The symptoms did not recur at any subsequent dose.

There were no renal or neurologic AEs observed in this trial.

#### 6.2.12.6 Clinical Test Results

Two adverse events in two subjects were related to clinical lab abnormalities. One is described above: increased serum ferritin. The second is a subject with decreased hemoglobin levels and red blood cell count. Anemia was reported and judged to not likely be due to the study drug. The subject recovered from the event.

#### 6.2.12.7 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

#### 6.2.13 Study Summary and Conclusions

Hemostatic effect of REBINYN during surgery was confirmed. As per the primary endpoint, the success rate was 100% in 13 surgeries (9 major and 4 minor) judged to be 3 good and 10 excellent. A pre-operative dose of 80 IU/kg dose of REBINYN was effective. No subjects required additional doses on the day of surgery. One subject did not require any doses of REBINYN during the post-surgery days 1 to 6, while for the remaining 12 subjects, the mean number of doses was 2.2 (median: 2.0) ranging from 1 to 4 doses. The mean dose was 41.1 IU/kg ranging from 20.0 to 42.4 IU/kg. One dose of 20.0 IU/kg was given and otherwise all other doses were nominally 40 IU/kg ranging from 41.0 to 42.4 IU/kg. In the post-surgery days 7 to 13, three subjects had completed the trial and one subject did not require additional doses during this period. For the remaining nine subjects, the mean number of doses was 1.7 (median: 2.0) ranging from 1 to 3 doses. The mean dose was 41.9 IU/kg ranging from 41.2 to 42.4 IU/kg. Two subjects (15.4%) received blood transfusions. Seven subjects (53.8%) had a median post-surgical drainage volume of 80.0 mL ranging from 0 to 2500 mL. Three subjects (23.1%) developed wound hematomas. None of the hematomas needed evacuation. Of the 13 exposed subjects, nine subjects (69.2%) had 16 adverse events. None of the adverse events were serious or severe. None of the adverse events led to withdrawal. Two adverse events (pruritus and increased serum ferritin) in two subjects (15.4%) were evaluated to be possibly or probably related to REBINYN by the investigator. No FIX inhibitors were detected and no thromboembolic events occurred.

One subject was positive for anti-HCP antibodies at trial entry and had received REBINYN in Study 3775 prior to transfer to the Surgery Study. The antibody titer was low and declined during the trial. There were no associated clinical signs or symptoms associated with this finding. Results of safety laboratory parameters and other safety-related examinations did not indicate clinically relevant changes as a result of REBINYN treatment.

*Reviewer Comment: Since perioperative use of this product would also be short-term, the recommendation is to approve this indication as the effects of PEG may only be seen after long-term exposure. As stated, this reviewer acknowledges that the data to support perioperative management of bleeding is limited. However, based on the risk/benefit profile including the short duration of exposure and total dose necessary for*

management of bleeding during the operative and post-operative phase, it is reasonable to assume that the safety profile favors marketing approval of REBINYN.

### 6.3 Trial #3: NN7999-3774

Safety, Efficacy and Pharmacokinetics of REBINYN in Previously Treated Children with Hemophilia B

Clinical Trials Identifier: NCT01467427

Initiated: May 16, 2012 Trial Completed: April 7, 2014

#### 6.3.1 Objectives

The primary objective was to evaluate the immunogenicity of REBINYN.

The secondary objectives were to evaluate: safety other than immunogenicity; to evaluate the efficacy of REBINYN in long term prophylaxis and in the treatment of breakthrough bleeding episodes; to evaluate the efficacy of REBINYN through FIX activity level; to evaluate the PK properties of REBINYN; and to evaluate patient reported outcomes (PROs) and assess health economic impact of treatment with REBINYN.

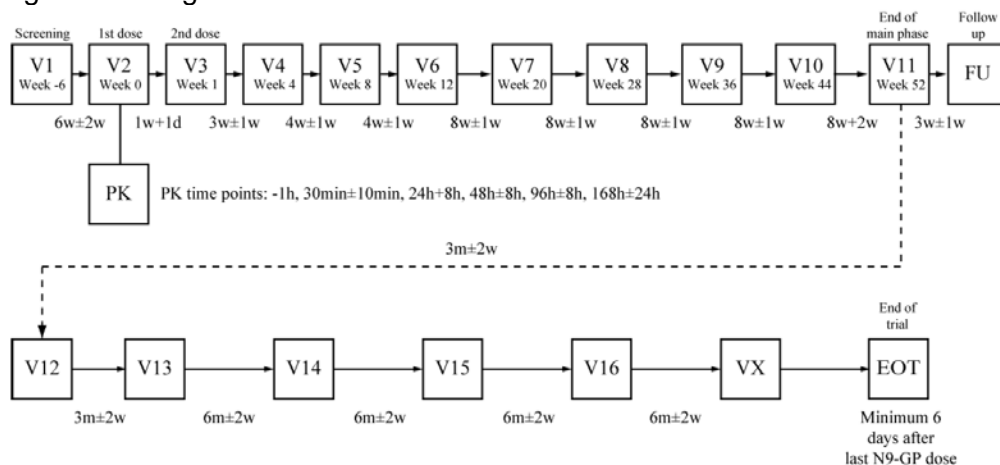
#### 6.3.2 Design Overview

This was a multicenter, multinational, open label, non-controlled, single arm, confirmatory trial evaluating safety, efficacy and pharmacokinetics of REBINYN in prophylaxis and on demand treatment of bleeding episodes in children with hemophilia B.

The trial was divided into a main phase of 52 weeks followed by an optional extension phase. The subjects received an initial dose of 40 IU/kg followed by PK assessment. The second dose was administered at the trial site and then administered weekly at home.

Please see below for design overview.

Figure 5: Design Overview



Source: BLA125611/0 CSR 3774 Figure 9-1 page 31/455

### 6.3.3 Population

The trial enrolled previously treated children  $\leq 12$  years with hemophilia B and FIX activity level  $\leq 2\%$ . The subjects were stratified into two age groups: 0-6 years and 7-12 years. A minimum of 10 subjects in each age group were planned to complete the main phase with at least 50EDs. Subjects 0-6 years were not included in the study until PK data for the older age cohort had been evaluated.

The key inclusion criteria are below:

1. Male patients with moderately severe or severe congenital hemophilia B with a FIX activity level  $\leq 2\%$  according to medical records.
2. Age  $\leq 12$  years (until patient turns 13 years, at time of inclusion).
3. Body weight  $\geq 10$  kg
4. History of at least 50 EDs to other FIX products.

The key exclusion criteria are below:

1. Known or suspected hypersensitivity to FIX, hamster protein or related products.
2. Known history of FIX inhibitors based on existing medical records, laboratory report reviews and patient/caregiver interviews.
3. Current FIX inhibitors  $\geq 0.6$  BU (central laboratory).
4. Platelet count  $< 50,000/\mu\text{L}$  at screening (local laboratory).
5. Alanine aminotransferase (ALT)  $> 3$  times the upper limit of normal reference ranges at screening (central laboratory).
6. Creatinine level  $\geq 1.5$  times above the upper normal limit of normal reference ranges at screening (central laboratory).
7. HIV positive, defined by medical records, and with a CD4+ lymphocyte count  $\leq 200/\mu\text{L}$ .
8. Immune modulating or chemotherapeutic medication (except single pulse treatment-, inhaled and topical steroids).
9. Previous arterial thrombotic events (myocardial infarction and intracranial thrombosis, as defined by medical records).

Study withdrawal criteria included the following:

1. Development of FIX inhibitors  $> 5$  BU confirmed by two consecutive samples at the central laboratory.
2. Anaphylactic reaction to the investigational product.
3. Major surgery (exception is placement of central venous access port).
4. Significant thromboembolic event.
5. Incapacity or unwillingness to follow trial procedures.

### 6.3.4 Study Treatments or Agents Mandated by the Protocol

As above in Section 6.1.4

### 6.3.5 Directions for Use

REBINYN was dosed once weekly 40 IU/kg for prophylaxis. Bleeding episodes were treated as soon as they were identified and dosed with a single dose of 40 IU/kg. Severe bleeding episodes were treated immediately with 80U/kg.

REBINYN was supplied as freeze-dried powder in single-use vials with a nominal content of 2000 U/vial to be reconstituted with 4.2 mL of histidine solvent for IV injection.

This higher dose from the phase 3 study in adults was chosen as the clearance was expected to be higher in children. Therefore, the higher of the two dose levels was chosen.

Surgeries were included in this trial.

#### 6.3.6 Sites and Centers

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

#### 6.3.7 Surveillance/Monitoring

Prior to any assessments, baseline PRO data was collected. All laboratory assessments were done at Visit 1.

Visit 2-first dosing of REBINYN and PK visit at the trial site.

Visit 3-The second dose was administered at the trial site after last PK sample had been collected; Prophylactic home treatment was initiated after the trial site dose

Visit 4-6-Patients received study drug every fourth week at the trial site

Visit 7-10-Patients received study drug every eighth week at the trial site

Visit 11-Follow up visit and end of main phase with an option to continue on extension phase

#### 6.3.8 Endpoints and Criteria for Study Success

All bleeding episodes and treatment of bleeding episodes were recorded in the medical records. The severity of bleeding episodes was defined as:

- Mild/Moderate: Bleeding episodes that were uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal- or subcutaneous bleeds.
- Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeds were categorized as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the hemoglobin level (>3g/dL) were also reported as severe. These bleeding episodes were to be treated immediately at home or at the local emergency room and the trial personnel were to be contacted.

The assessment for hemostatic response was made by the subject or parent/caregiver. If there was no observed effect, the investigator was contacted prior to the second dose. If the bleed was classified as a severe bleed, a dose of 80U/kg was given. The four point scale below was used to assess hemostatic response:

- Excellent – abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single infusion.
- Good – noticeable pain relief and/or improvement in signs of bleeding within 8 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 infusion within 8 hours.
- Poor – no improvement or worsening of symptoms within 8 hours after two injections.

#### 6.3.9 Statistical Considerations & Statistical Analysis Plan

The primary endpoint was a safety endpoint: incidence of inhibitors against Factor IX. The rate of neutralizing inhibitors was reported and a 1-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. Evaluation of

all other endpoints was based on descriptive analysis. The trial had no confirmatory secondary endpoints.

The main phase of the trial was analyzed and reported before completion of the extension phase.

#### 6.3.10 Study Population and Disposition

A total of 28 subjects were screened for this trial and 25 subjects were enrolled. The three subjects were screening failures due to exclusion criteria of diagnosis of obesity (two subjects) and known history of FIX inhibitors (one subject). Twelve subjects were in the 0-6 year's age group and 13 subjects were in the 7-12 years age group.

##### 6.3.10.1 Populations Enrolled/Analyzed

Of the 25 enrolled, 24 subjects completed the main phase of the trial. One subject was withdrawn and all but 2 subjects continued in the extension phase of the trial. The 2 that withdrew at the end of the main phase was due to the unwillingness to follow trial procedures. All 25 were included in the PK assessment. Three total subjects had missing data in the PK assessment.

##### 6.3.10.1.1 Demographics

The trial population consisted of males with hemophilia B and a median age of seven years (ranging from 1 to 12 years old. Of the 25 exposed subjects, 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 ten years. The majority of the patients were White (N=13, 52.0%) and the second-largest group was Asian (N=8, 32.0%).

Table 17: Demographics of Pediatric Trial

	0-6 years	7-12 years	Total
Number of Subjects	12	13	25
Age at baseline(years) 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
United States (%)	3 (25.0)	6 (46.2)	9 (36.0)
Ethnicity			
Hispanic or Latino (%)	-	2 (15.4)	2 (8.0)
Race (%)			
Asian	4 (33.3)	4 (30.8)	8 (32.0)
Black	-	1 (7.7)	1 (4.0)
White	8 (66.7)	5 (38.5)	13 (52.0)
Other	-	3 (23.1)	3 (12.0)

Source: Adapted from BLA125611/0 CSR 3774 Table 10-3 page 88/455

##### 6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects were males with severe Hemophilia B and a FIX level <1.0%. All were PTPs with a history of at least 50 EDs to other FIX products. Prior to enrollment in the trial, 22 of the 25 subjects (88%) were on prophylactic treatment, whereas three (12%) of the

subjects were on the on-demand treatment. The median ABR for treatment-requiring bleeds for subjects previously on prophylaxis was 2.0. Previous on-demand subjects had a median ABR for treatment-requiring bleeds of 9.0.

Two (8.0%) of the subjects in the 7-12 year age group had target joints at baseline.

#### 6.3.10.1.3 Subject Disposition

There were a total of 155 protocol deviations that were reported. Three were at the trial level, 12 were at the trial unit level, and 140 were at the subject level.

Table 18: Protocol Deviations

<b>Deviation</b>	<b>Number of deviations</b>
Informed consent	9
Assessment deviations (incl. lab)	76
Treatment compliance	28
Trial product handling/trial product issues	13
Visit window	5
Withdrawal criteria	1
Other/miscellaneous issues	8
<i>Total</i>	<i>140</i>

Source: BLA125611/0 CSR 3774 Table 10-8 page 96/455

#### 6.3.11 Efficacy Analyses

The efficacy analysis was performed on all 25 subjects enrolled.

##### 6.3.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was the incidence of inhibitory antibodies against FIX, a safety endpoint. Please see the safety analysis below.

##### 6.3.11.2 Analyses of Secondary Endpoints

Fifteen subjects were treated for a total of 42 bleeds during the trial. Ten subjects did not have bleeds. In the older age group (7-12 years), 10 subjects experienced bleeds requiring treatment, whereas there were 5 subjects in the younger age group. Twenty-five of the bleeds were traumatic (60%), 13 were spontaneous (31%), and 4 were classified as of other origin (10%). The most frequent location was in the joint in the older age group and subcutaneous bleeds in the younger age group. Two of the 42 bleeds resulted in re-bleeds.

The mean duration of bleeds in the younger age group was 83.9 hours and 35.4 hours in the older age group.

*Reviewer Comment: In the younger age group, the duration of bleeds ranged from 1.1 to 666.3 hours. The subject with the longest duration had either a spontaneous or traumatic cutaneous bleed and treated with a total of 5 injections over a 7 day period. The treatment response was rated as poor. The bleeding was reported as stopped after 21 days.*

*In the older age group, the duration of bleeds ranged from 1.4 to 119 hours. The subject with the longest bleed had a mild traumatic left elbow joint bleed and was treated twice and then resumed prophylaxis. It was reported that the bleed continued over a 5 day period.*



The detail of bleeds is in the table below:

Table 19: Details of Bleeds

	0-6 years	7-12 years	Total
Number of subjects with bleeds	5	10	15
Number of bleeds	11	31	42
Cause of bleed (%)			
Spontaneous	3 (27.3)	10 (32.3)	13 (31.0)
Traumatic	8 (72.7)	17 (54.8)	25 (59.5)
Other	-	4 (12.9)	4 (9.5)
Site of Bleed, N (%)	11 (100)	31 (100)	42 (100)
Joint	2 (18.2)	13 (41.9)	15 (35.7)
Classification of bleed			
Mild/Moderate	11 (100)	31 (100)	42 (100)
Severe	-	-	-
Time since last dose N, (%)	119 (100)	66 (100)	185 (100)
≤4 days	3 (27.3)	8 (36.4)	11 (33.3)
≥ 4 days	8 (72.7)	14 (63.6)	22 (66.7)

Source: Adapted from BLA125611/0 CSR 3774 Table 11-1 page 101/455

*Reviewer Comment: It is unclear what "other" entails in the Table above under Cause of bleeds. In the data listings, majority are noted as mucosal bleeds in addition to a few muscular bleeds.*

*Despite the higher clearance in children (PK section below), the percentage of spontaneous bleeds were less than in adults. This may be because children are prone to traumatic bleeds.*

The ABR was calculated from the breakthrough bleeds which was 1.44 for the entire population. For spontaneous bleeds, it was 0.45 and 0.86 for traumatic bleeds. For subjects previously on prophylaxis (n=22), the estimated ABR was 1.38 compared to 2.51 (mean bleeding rate during last 12 months prior to trial). For subjects previously on on-demand (n=3) treatment, the estimated ABR was 1.89 compared to 10.3 (mean bleeding rate during last 12 months prior to trial).

Table 20: Annualized Bleeding Rate

	0-6 years	7-12 years	Total
ABR (N)	12	13	25
Mean (SD)	0.83 (1.13)	1.96 (1.88)	1.42 (1.64)
Median	0	2.0	1.0
Poisson Estimate of ABR (95% CI)	0.87 (0.38;2.01)	1.88 (1.14;3.09)	1.44 (0.92; 2.26)

Source: Adapted from BLA125611/0 CSR 3774 Table 11-2 page 102/455

The hemostatic response after treatment of a bleed was evaluated on a 4 point scale. All of the 42 bleeds were rated and the success rate was 92.9%.

Table 21: Hemostatic Response and Success Rate- Full Analysis Set

	0-6 years	7-12 years	Total
Number of subjects with bleeds (%)	5 (41.7)	10 (76.9)	15 (60.0)
Hemostatic Response, N (%)	11 (100)	31 (100)	42 (100)
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)
Missing	2 (1.5)	1 (1.4)	3 (1.5)

Source: BLA125611/0 CSR 3774 Table 11-7 page 105/455

For spontaneous bleeds, the success rate was 84.6%. The success rate for traumatic bleeds was 96%. The rate was similar in the two age groups for traumatic bleeds. The rate for spontaneous bleeds was lower in the youngest age group. Three spontaneous bleeds occurred in the younger age group and one was rated as a failure.

The rate for subjects who had been on prophylaxis was 91.4%. Those that were on on-demand had a success rate of 100%.

Table 22: Number of Bleeds

Factor	Number of bleeds <sup>a</sup>	Success rate
<b>Cause of bleed</b>		
Spontaneous	13	84.6
Traumatic	25	96.0
<b>Previous treatment</b>		
Prophylaxis	35	91.4
On-demand	7	100.0
<b>Location of bleed</b>		
Joint	16	87.5
Target joint <sup>b</sup>	2	100.0
Subcutaneous	10	90.0
Mucosal	8	100.0
Muscular	8	100.0
Gastrointestinal	1	100.0
Other	3	100.0
<b>Time from start of bleed until the first administration of nonacog beta pegol</b>		
< 2 hours	16	87.5
2-4 hours	9	88.9
> 4 hours	9	100.0
<b>Number of injections to treat bleed</b>		
1 injection	36	97.2
2 injections	5	80.0
5 injections	1	0.0

a: Number of bleeds with a haemostatic evaluation; b: Target joints are included in joint bleeds

Source: BLA125611/0 CSR 3774 Table 11-8 page 106/455

The majority of bleeds were resolved with 1 injection in both age groups. In 36 cases, one injection was used to treat a bleed.

The PK endpoints of the two age groups were comparable with a slightly higher clearance in the younger age group. After the single dose of nonacog beta pegol, the

FIX activity 30 min post dosing was 0.543 U/mL in the 0–6 years age group and 0.596 U/mL in the 7–12 years age group. The single dose FIX trough activity level was 0.084 U/mL in the 0–6 years age group and 0.109 U/mL in the 7–12 years age group. The clearance was 0.758 mL/h/kg in the 0–6 years age group and 0.650 mL/h/kg in the 7–12 years age group and the incremental recovery was 0.015 (U/mL)/(U/kg) and 0.016 (U/mL)/(U/kg) in the 0–6 years age group and 7–12 years age group respectively. The terminal half-life for the entire subject population was 73.0 h, 69.6 h in the 0–6 years age group and 76.3 h in the 7–12 years age group. Please refer to Clinical Pharmacology Review for a detailed analysis.

A total of 2 minor surgeries were performed during the trial.

#### 6.3.11.3 Subpopulation Analyses

N/A

#### 6.3.11.4 Dropouts and/or Discontinuations

One subject was withdrawn from the main phase after 3.5 months with 10 ED due to withdrawal of consent. There were no dropouts or discontinuations due to adverse events.

#### 6.3.11.5 Exploratory and Post Hoc Analyses

Questionnaires were distributed to subjects and their parents. Overall, both subjects and parents reported a slight worsening in the mean total score of the HAEMO-QOL in the 4-7 years age group, whereas a slight improvement was reported by both subjects and parents in the 8-12 years age group. No total score could be calculated for the TAPQOL, which was used for children aged 0-3 years. The PRO results were not statistically significant.

#### 6.3.12 Safety Analyses

##### 6.3.12.1 Methods

A total of 25 subjects were exposed to the study drug. All evaluations of safety were based on all 25 subjects.

##### 6.3.12.2 Overview of Adverse Events

There were no apparent differences in the safety-related results among the two different age groups. A total of 250 adverse events were reported for 23 of the subjects. All of the events were mild or moderate severity and 242 out of 250 were judged by the investigator unlikely to be related to REBINYN. There were no severe events.

The primary safety endpoint of this trial was incidence of inhibitors. There were no inhibitors detected in the trial. No anti- REBINYN binding antibodies or anti-PEG antibodies were detected.

Anti-HCP antibodies were reported in one subject at Visit 11 with a titer of one. There were no associated AEs reported, and this subject continued to the extension phase of the trial.

No AE led to withdrawal of any subject. No thromboembolic events or medication errors were reported.

The most commonly reported adverse events in this trial were contusion (17 events in 8 patients [32.0%]), excoriation (10 events in 5 patients [20.0%]), nasopharyngitis (11 events in 5 patients [20.0%]), cough (17 events in 10 patients [40.0%]), vomiting (10 events in 4 patients [16.0%]) and pyrexia (14 events in 6 patients [24.0%]).

A total of 8 AEs in 4 subjects were judged to be related to the study drug. These included gastrointestinal symptoms including abdominal pain, diarrhea, and nausea. Other AEs reported were infusion/injection site pain, eosinophilia, headache, and wheezing.

*Reviewer Comment: This clinical reviewer agrees that these adverse events could have possible relation. All of the AEs resolved.*

#### 6.3.12.3 Deaths

There were no deaths reported.

#### 6.3.12.4 Nonfatal Serious Adverse Events

There was one serious AE regarding food poisoning and not related to the study drug.

#### 6.3.12.5 Adverse Events of Special Interest (AESI)

One event of wheezing was reported as a AE of special interest as it was judged to an allergic reaction with possible relation to the study drug. The other event was a mild rash in the armpit and was considered unrelated.

#### 6.3.12.6 Clinical Laboratory Test Results

Clinical lab results reported as AEs included increased international normalized ratio in 1 (4.0%) patient (b) (6), prolonged prothrombin time in 1 (4.0%) subject, palpable lymph nodes in 1 (4.0%) subject, positive varicella virus test in 1 (4.0%) subject and eosinophilia in 1 (4.0%) subject. All events were judged to be unlikely related to REBINYN, except the event of eosinophilia, which was judged to be possibly related to REBINYN by the investigator.

There were three lab results that were not reported as AEs but clinically significant. These included a high WBC count in 2 subjects and one with a high neutrophil count.

#### 6.3.12.7 Dropouts and/or Discontinuations

None

#### 6.3.13 Study Summary and Conclusions

The primary endpoint was incidence of inhibitors against FIX defined as titer  $\leq 0.6$  BU. No inhibitors were detected. A total of 250 adverse events were reported in 23 (92%) subjects exposed to REBINYN. All of the adverse events were of mild (240 events) or moderate (10 events) severity. The most commonly reported adverse events were contusion (17 events in 8 subjects [32.0%]), excoriation (10 events in 5 subjects [20.0%]), nasopharyngitis (11 events in 5 subjects [20.0%]), cough (17 events in 10 subjects [40.0%]), vomiting (10 events in 4 subjects [16.0%]) and pyrexia (14 events in 6 subjects [24.0%]). No subjects were withdrawn due to adverse events. There were no deaths. No safety issues were detected in the pediatric study; however there are still safety concerns related to the PEG accumulation in the choroid plexus as noted in the pre-clinical studies.

A total of 15 subjects (60.0%) were treated for a total of 42 bleeds during the trial. All bleeds were classified as mild/moderate and the majority (N=25, 59.5%) were traumatic. The success rate for treatment of all bleeds was 92.9%. A total of 89.7% of all successfully treated bleeds were treated with one injection only. The mean dose (in IU/kg/bleed) for treating a bleed was 59.7 in the younger age group and 47.5 in the older age group. The estimated ABR in the trial was 1.44 bleeds/patient/year (median ABR was 1.0 bleeds/patient/year). For spontaneous bleeds the ABR was 0.45 bleeds/patient/year and 0.86 bleeds/patient/year for traumatic bleeds. For patients previously on prophylaxis treatment the estimated ABR during the trial was 1.38 bleeds/patient/year as compared to a historical ABR of 2.51 bleeds/patient/year. The estimated ABR for patients previously on on-demand treatment was 1.89 bleeds/patient/year as compared to an historical ABR of 10.3 bleeds/patient/year.

Reviewer Comment: There are no issues with the efficacy of this product for on demand treatment and routine prophylaxis in pediatrics. As with the adult trial, there is no clear safety signal from accumulation of PEGylation was observed in the clinical trials. The pediatric population is vulnerable to the potential effects of long-term administration of this product due to ongoing brain growth and development. Neurodevelopmental milestones were not specifically recorded in this study. Furthermore, only 12 subjects were less than 6 years of age, highlighting the paucity of data in the younger age cohort. Therefore, chronic use of this product would not be recommended with this uncertainty. Short-term use (on demand treatment and perioperative use) is unlikely to lead to accumulation of PEG or vacuolation in the choroid plexus. Prolonged exposure is not recommended and a specific duration of use cannot be included in the label, as the exposure to PEG accumulation in the animal studies are not available nor was the clinical study designed to evaluate exposure to PEG toxicity. As stated, there is limited data on the dose used in major/severe bleeding, and the dose of 80 IU/kg used in major surgeries can be extrapolated to be used in support of efficacy in the treatment of major bleeding events for the on demand treatment and control of bleeding episodes.

#### 6.4 Trial #4: NN7999-3775

Safety and Efficacy of REBINYN after Long-Term Exposure in Patients with Hemophilia B

Clinical Trials Identifier: NCT01395810

Initiated: April 16, 2012 Trial Completed: March 31, 2014

##### 6.4.1 Objectives

The primary objective was to evaluate the immunogenicity of REBINYN.

The secondary objectives included:

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

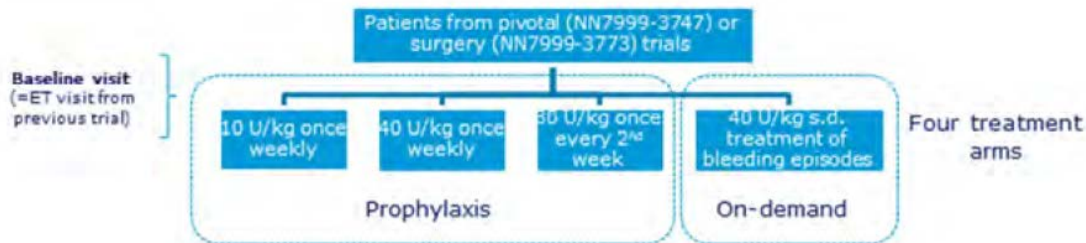
- To evaluate Patient Reported Outcomes (PRO), including health-related and disease-specific quality of life and patient treatment satisfaction
- To evaluate the health economic impact of REBINYN treatment

#### 6.4.2 Design Overview

The trial was an open label, non-randomized, multinational trial with the purpose of evaluating safety and clinical efficacy of treatment of bleeding episodes and for long term prophylaxis with REBINYN. Subjects enrolled could be recruited from the adult and adolescent trial or the surgery trial.

The trial included four different treatment arms: initially two prophylaxis treatment arms with 10 or 40 IU/kg REBINYN, and one on-demand treatment with 40 IU/kg. The third prophylaxis option of 80 IU/kg REBINYN dosed every two weeks was added as an amendment to the protocol. Surgery was allowed during this trial. The choice of treatment was decided by the subject and investigator.

Figure 6: Design Overview



Source: BLA125611/0 CSR 3775 Table 9-1 page 34/934

#### Reviewer Comment:

*Since subjects were not randomized to either the on-demand or prophylaxis treatment arm, it is difficult to make direct comparisons of treatment results between treatments arms, as some subjects switched arms. Due to potential dose selection bias, the data from Trial 3775 were not considered appropriate for pooling in the main efficacy evaluation of prophylaxis.*

#### 6.4.3 Population

Subjects with Hemophilia B, aged 13-70 years and a FIX activity of  $\leq 2\%$  were enrolled. The inclusion and exclusion criteria are similar to the criteria in Study 3747 and 3773. Please refer to Section 6.1.3 and 6.2.3.

#### 6.4.4 Study Treatments or Agents Mandated by the Protocol

The four treatments arms are above. Subjects could switch among treatment arms if agreed between subject and investigator.

#### 6.4.5 Directions for Use

Subjects with on-demand treatment and subjects on prophylaxis who experienced a bleeding episode were to treat with a single dose of 40 IU/kg, unless the episode was severe and then treated with 80 IU/kg.

The prophylaxis arms were targeted to give measurable FIX activity of  $\geq 1\%$  during the entire prophylaxis period. The maximum dose to be administered to a subject within 24

hours was 200 IU/kg with a maximum individual dose of 80 IU/kg to be administered no more frequently than every hour.

#### 6.4.6 Sites and Centers

A total of 48 sites in 16 countries obtained ethical committee/ health authority (EC/HA) approval to recruit patients. Ultimately, 41 sites in 15 countries enrolled patients.

#### 6.4.7 Surveillance/Monitoring

Monitoring was done throughout the trial to ensure the protocol was adhered to and all issues were recorded.

#### 6.4.8 Endpoints and Criteria for Study Success

The primary endpoint was the incidence of inhibitory antibodies against FIX, defined as titer  $\geq 0.6$  BU.

Secondary endpoints included:

- Hemostatic effect of REBINYN
- Number of bleeding episodes during routine prophylaxis
- FIX trough levels
- The number of injection of REBINYN required per bleeding episode
- The amount of REBINYN required per bleeding episode

#### 6.4.9 Statistical Considerations & Statistical Analysis Plan

All endpoints were summarized. No interim analysis was performed. The trial was shortened due to insufficient drug supplies.

#### 6.4.10 Study Population and Disposition

A total of 71 subjects were dosed during this trial. All subjects came from either the adult trial (66) or the surgery trial (5). There were 48 subjects treated on the 40 IU/kg prophylaxis arm at some point during the trial. A total of 14 subjects underwent surgery during the trial. Four of those subjects received 10 IU/kg and ten received 40 IU/kg per week. A total of nine subjects changed treatment arm during the trial. The remaining 62 stayed on the same treatment arm. Sixty-five subjects completed the trial.

##### 6.4.10.1 Populations Enrolled/Analyzed

No screening failures were reported. Six subjects were withdrawn from the trial. Two subjects were withdrawn due to the incapacity or unwillingness to follow trial procedures. Two were withdrawn due lost to follow up. One was withdrawn due to ineffective therapy. One was withdrawn due to death.

##### 6.4.10.1.1 Demographics

The trial population consisted of males with hemophilia B and a median (range) age of 32 (14-66) years. The majority of the subjects were White (67.6%) while 21.1% were Asian, 7.0% were Black or African American, and 4.2% were listed as "other". The trial population came from 15 countries world-wide.

##### 6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All 71 subjects in the trial were males with congenital hemophilia B and a FIX activity  $\leq 2\%$ . All subjects were previously treated patients with a history of at least 150 exposure days to other FIX products and no history of inhibitors.

A total of 190 protocol deviations were reported in this trial. There were 22 deviations at the trial site level and 167 at the patient level. The deviations at the patient level included the following categories: informed consent, inclusion/exclusion criteria, laboratory issues/samples, trial product handling, and treatment compliance.

*Reviewer Comment: None of the deviations impacted the ability to analyze the data.*

#### 6.4.11 Efficacy Analyses

##### 6.4.11.1 Analyses of Primary Endpoint(s)

No inhibitory antibodies against REBINYN were reported.

##### 6.4.11.2 Analyses of Secondary Endpoints

There were a total of 207 bleeds. The on-demand group had 73 bleeding episodes. A total of 134 bleeding episodes were reported for 44 of the 67 subjects on prophylaxis. ABRs for subjects on the same treatment arm for more than three months were calculated, in which there were a total of 198 bleeds. Subjects who changed arms are counted in multiple treatment regimens. Twelve (12) subjects from the 10 IU/kg arm and 22 subjects from the 40 IU/kg arm of Trial 3747 chose to continue with the same prophylaxis dose throughout Trial 3775. Fourteen (14) subjects switched from 10 IU/kg to 40 IU/kg either at the start of, or during, Trial 3775, while 3 subjects switched from 40 IU/kg to 10 IU/kg during this time. The ABRs are below in the Table below.

Table 23: Annualized Bleeding Rate

	10 IU/kg	40 IU/kg	80 IU/kg biweekly	All	On- Demand	Total
Number of subjects on Same Treatment ≥3months	20	49	-	66	5	70
Subjects with Bleeds (%)	12 (70)	29 (59.2)	1(50)	43 (65.2)	5 (100)	48 (68.6)
All bleeds, N	35	91	1	134	73	207
Median ABR	1.36	1.00	-	1.05	12.82	1.11
Spontaneous Bleeds, N	25	36	-	61	68	129
Median ABR	1.05	0.00	-	0.00	11.96	0.00
Traumatic Bleeds, N	10	48	1	59	5	64
Median ABR	0.00	0.00	-	0.00	0.74	0.00

Source: BLA125611/0 CSR 3775 Table 11-2 page 89/934

The median ABR [IQR] was 1.36 [0; 2.23] and 1.0 [0; 2.03] for the 10 IU/kg and 40 IU/kg groups, respectively. The median ABR [IQR] for the on-demand group was 12.82 [12.67;13.02]. Most bleeds were confined to the joints. These bleeds were all characterized as mild or moderate bleeds. There were 207 total bleeds and 87.9% resolved with 1 injection of REBINYN. The highest number of injections to treat a bleed was four injections which occurred once. The mean dose used in the 40 IU/kg prophylaxis group was 42.1 IU/kg.



*Reviewer Comment: Since subjects who switched study arms are counted in multiple treatment regimens and therefore the reported ABR in this study represents the ABR based on multiple treatment regimens from any of the categories listed in the table above. Subjects could remain on a particular regimen for a short period of time, for example switch from on-demand to 10 IU/kg prophylaxis and switch to 40 IU/kg. Thus the interpretation of the results from the extension trial is subject to selection bias and short exposures. Cautious interpretations of the results are therefore necessary. It appears that there were more traumatic bleeds in the 40 IU/kg group, which are different when compared to Trial 3747. This could be due to subjects switching arms selectively based on the number of spontaneous bleeding rates. As stated, the applicant reports trough levels approaching 40%, and yet up to one-third of subjects are reporting a spontaneous bleed.*

There were 11 treatment failures of bleeding episodes. Nine were characterized as moderate and 2 as poor. The treatment failures occurred only in adults. Ten out of the 11 cases were following spontaneous bleeds in subjects who were on on-demand treatment before first trial entry.

*Reviewer Comment: This may be an appropriate response, as these subjects were on-demand and may not have sufficient FIX levels to adequately control the bleeding episode.*

Fourteen subjects underwent 24 surgical procedures. There were 11 dental procedures, five endoscopies, four skin incisions, drainage and excisions, and two orthopedic surgeries, one cataract surgery, and one port-a-catheter removal.

Twenty of the 24 surgical procedures were recorded as “excellent”, two as “good” and the remaining two were not determined.

*Reviewer Comment: Based on the surgical procedures, the two orthopedic surgeries and cataract surgery were considered major surgical procedures.*

Within each treatment arm, change in patient reported outcome (PRO) scores were calculated for those subjects who did not switch treatment arms during the trial. PROs indicated improvement or at least sustained health –related quality of life from baseline to end of trial for those in the prophylaxis treatment arms.

#### 6.4.11.3 Subpopulation Analyses

N/A

#### 6.4.11.4 Dropouts and/or Discontinuations

Six subjects were withdrawn from the trial. Two subjects were withdrawn due to the incapacity or unwillingness to follow trial procedures. Two were withdrawn due lost to follow up. One was withdrawn due to ineffective therapy. One was withdrawn due to death.

Please see above Section 6.4.10.1 for details.

#### 6.4.11.5 Exploratory and Post Hoc Analyses

N/A

#### 6.4.12 Safety Analyses

A total of 71 subjects were exposed to REBINYN.

##### 6.4.12.1 Methods

All evaluations of safety were based on the safety analysis set, including all 71 dosed subjects which was the full analysis set.

##### 6.4.12.2 Overview of Adverse Events

The primary endpoint was incidence of inhibitors against FIX. No inhibitory antibodies against REBINYN were reported.

Two subjects had a positive binding antibody titer for REBINYN without any inhibitory effect. These were transient and low titers. Four subjects had anti-CHO HCP antibodies. No thromboembolic events were reported.

A total of 155 AEs were reported for 49 subjects exposed. The most commonly reported AEs were nasopharyngitis and influenza. The majority (96%) of the adverse events were mild or moderate.

*Reviewer Comment: There were four AEs that were judged to be related to the study drug. These included an injection site rash due to the temporal nature, two AEs were overdoses of the study drug, one AE was a case of neutropenia that could possibly be related to the study drug. All of these events recovered.*

A total of six severe adverse events were reported for three subjects. One subject had 4 of these events including musculoskeletal pain, arthralgia, and abdominal pain due to the subject's underlying condition of hepatocellular carcinoma. The second subject's AE was sarcoidosis and the third subject had gastroenteritis. The first subject died. The second and third subject's AEs recovered.

*Reviewer Comment:*

*None of the SAEs were judged to be related to the study drug.*

##### 6.4.12.3 Deaths

There was one death in this trial. The subject was in the 40 IU/kg treatment arm and diagnosed with metastatic stage IV hepatocellular carcinoma after 17 EDs of REBINYN.

*Reviewer Comment: This death was judged not to be due to the study drug.*

##### 6.4.12.4 Nonfatal Serious Adverse Events

There were six serious AEs. Two of the serious AEs were also severe which included the subject with hepatocellular carcinoma and the subject with gastroenteritis. The other four serious AEs included a road traffic accident, faecaloma, local swelling, and a femur fracture. All of these serious events recovered except the subject who died.

##### 6.4.12.5 Adverse Events of Special Interest (AESI)

No inhibitory antibodies were reported, no thromboembolic events were reported. One subject experienced an injection site rash after 20 EDs with REBINYN. This event resolved after the subject stopped using alcohol wipes at the injection site.

A total of five medication errors were reported. These included three overdoses, one incorrect route of drug administration, and an administration of non-reconstituted histidine. All errors had mild to moderate severity and the AE recovered.

*Reviewer Comment: The events related to the rash or dosing errors are anticipated and of low frequency and therefore will not be included in the labeling.*

#### 6.4.12.6 Clinical Laboratory Test Results

A total of 7 AEs were observed for 4 subjects in the 40 IU/kg prophylaxis arm as follows:

- increased levels of gamma-glutamyltransferase, aminotransferases, and neutropenia.

*Reviewer Comment: This subject was tested positive for hepatitis C antibodies at the baseline visit for this trial.*

- Increased level of C-reactive protein
- Decreased levels of blood testosterone
- Eosinophilia

All AEs were non-serious and mild in severity.

#### 6.4.12.7 Dropouts and/or Discontinuations

One subject was withdrawn due to an AE of hepatocellular carcinoma. This subject died due to this AE.

#### 6.4.13 Study Summary and Conclusions

No safety issues were identified, and no thromboembolic events or inhibitors were reported. The hemostatic effect of REBINYN was confirmed with an overall success rate for treatment of bleeds of 94.6%. The estimated ABR was 1.84 (95% CI: 1.33; 2.56) among all subjects on prophylaxis.

*Reviewer Comment: As stated previously, there are no issues with the efficacy of this product for on demand treatment. In this extension study, no clear safety signal from accumulation of PEG was observed. Overall, some subjects were exposed to the study drug for more than 3 years, however there were only 12 subjects less than 6 years of age and only 2 subjects over age 60.*

*Given the preclinical findings of PEG accumulation in the choroid plexus, the younger pediatric and geriatric patient population may be vulnerable to neurologic dysfunction, especially infants and children who have developing brains and in patients who are cognitively impaired with long term use. Although the clinical implications of the animal findings are not clear as there was no specific signal identified in the clinical studies (which were not specifically designed to assess for neurocognitive function), the duration of use, cumulative dose, age of the patient, and related comorbidities that may increase the neurologic risks to patients exposed to Rebinyn need to be considered when administering this product. It is unclear whether neurocognitive assessments would be useful. These potential risks will be addressed in the label.*

## 7. INTEGRATED OVERVIEW OF EFFICACY

Four trials have evaluated the clinical efficacy of REBINYN, and these were

designed as multicenter, non-controlled trials investigating the safety and efficacy of REBINYN for prophylaxis, treatment of bleeds, and perioperative management, in previously treated male patients (PTPs) with severe or moderate hemophilia B (FIX activity <2%).

## 7.1 Indication #1 On-Demand Treatment and Control of Bleeding Episodes.

### 7.1.1 Methods of Integration

Please see Section 6 above for key inclusion and exclusion criteria.

### 7.1.2 Demographics and Baseline Characteristics

All subjects were male. The median age was 23 years from all the studies. Subjects who were treated with on demand therapy included: one subject (0-6 years); two subjects (7-12 years); our subject (13- 17 years); thirty-seven subjects (18-70 years).

Table 24: Baseline Demographics

	0-6 years	7-12 years	13-17 years	18-70 years	Total
Number of patients	12	13	18	62	105
Age at baseline in first trial (year)					
N	12	13	18	62	105
Mean (SD)	3.1 ( 1.7)	9.6 ( 1.6)	14.8 ( 1.4)	36.5 ( 11.9)	25.7 ( 16.3)
Median	3.0	10.0	15.0	34.5	23.0
Min ; Max	1 ; 6	7 ; 12	13 ; 17	18 ; 65	1 ; 65
Country, N (%)					
N	12 (100.0)	13 (100.0)	18 (100.0)	62 (100.0)	105 (100.0)
Canada	1 ( 8.3)	3 ( 23.1)	-	-	4 ( 3.8)
France	-	-	-	2 ( 3.2)	2 ( 1.9)
Germany	1 ( 8.3)	-	1 ( 5.6)	3 ( 4.8)	5 ( 4.8)
Italy	1 ( 8.3)	-	1 ( 5.6)	2 ( 3.2)	4 ( 3.8)
Japan	1 ( 8.3)	2 ( 15.4)	-	8 ( 12.9)	11 ( 10.5)
Macedonia	-	-	-	4 ( 6.5)	4 ( 3.8)
Malaysia	-	2 ( 15.4)	-	4 ( 6.5)	6 ( 5.7)
Netherlands	-	-	-	3 ( 4.8)	3 ( 2.9)
Romania	-	-	-	1 ( 1.6)	1 ( 1.0)
Russia	-	-	3 ( 16.7)	2 ( 3.2)	5 ( 4.8)
South Africa	-	-	-	4 ( 6.5)	4 ( 3.8)
Taiwan	2 ( 16.7)	-	-	1 ( 1.6)	3 ( 2.9)
Thailand	-	-	1 ( 5.6)	3 ( 4.8)	4 ( 3.8)
Turkey	-	-	2 ( 11.1)	2 ( 3.2)	4 ( 3.8)
United Kingdom	3 ( 25.0)	-	2 ( 11.1)	8 ( 12.9)	13 ( 12.4)
United States of America	3 ( 25.0)	6 ( 46.2)	8 ( 44.4)	15 ( 24.2)	32 ( 30.5)
Ethnicity, N (%)					
N	12 (100.0)	13 (100.0)	18 (100.0)	62 (100.0)	105 (100.0)
Hispanic or Latino	-	2 ( 15.4)	2 ( 11.1)	1 ( 1.6)	5 ( 4.8)
Not Hispanic or Latino	12 (100.0)	11 ( 84.6)	16 ( 88.9)	61 ( 98.4)	100 ( 95.2)
Race, N (%)					
N	12 (100.0)	13 (100.0)	18 (100.0)	62 (100.0)	105 (100.0)
White	8 ( 66.7)	5 ( 38.5)	15 ( 83.3)	37 ( 59.7)	65 ( 61.9)
Black	-	1 ( 7.7)	-	6 ( 9.7)	7 ( 6.7)
Asian	4 ( 33.3)	4 ( 30.8)	1 ( 5.6)	16 ( 25.8)	25 ( 23.8)
Other	-	3 ( 23.1)	2 ( 11.1)	3 ( 4.8)	8 ( 7.6)

Patients in 3775 are not included as their baseline information is as in the first trial, i.e. either 3747 or 3773.

From Trial 3773, only patients not previously treated in 3747 are included.

Source: BLA 125611/0 Module 2.7.3 Summary of Clinical Efficacy Table 3-2 page 39/80

### 7.1.3 Subject Disposition

The two trials that evaluated on demand treatment include the adult and adolescent trial (Study 3747) and pediatric trial (Study 3774). Fifteen subjects were exposed to REBINYN. Thirteen subjects in the on-demand treatment arm completed the trial. Two subjects discontinued the trial since they were withdrawn (one subject for ineffective therapy and one for personal reasons). None of the withdrawals were related to adverse events.

#### 7.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was a safety endpoint of immunogenicity. The primary endpoint in Trials 3747, 3775 and 3774 was incidence of inhibitory antibodies (inhibitors) against FIX. An inhibitor was defined as a titer  $\geq 0.6$  BU.

Please refer to the Integrated Overview of Safety for this discussion.

#### 7.1.5 Analysis of Secondary Endpoint(s)

- 1) 40 IU/kg dose: This dose was used for on demand treatment of minor/moderate bleeds and also used as the routine prophylaxis dose. This dose was shown to be efficacious as the majority of subjects in Trial 3747 only used one injection for treatment of a minor/moderate bleed. The 40 IU/kg dose was also used post-operatively to treat subjects undergoing major and minor surgeries. In the pediatric age group, the hemostatic response was considered a success in the majority of subjects in Trial 3774. These trials demonstrated efficacy with this dose post-operatively and for minor and moderate bleeds for all age groups.
- 2) 80 IU/kg: This dose was used preoperatively for major surgeries in Trial 3773 and Trial 3775. Although, as discussed, there was limited data with use of this dose for on-demand treatment of major bleeds, the data may be extrapolated from the surgery study to support the use of this dose in major bleeds, as it was shown efficacious in major surgeries. Moreover, 80 IU/kg should provide 80% peak FIX levels and with the long half-life should allow for adequate hemostasis in on demand treatment for major bleeds and for perioperative management for all age groups.

Reviewer's conclusion: As noted in Section 6.1.13, all of the bleeding events in the subjects in the on-demand group (n=13) were considered minor or moderate bleeding events and were treated at 40 IU/kg. The hemostatic efficacy for on-demand bleeding episodes was 94.4% based on achieving an excellent or good hemostatic response. 83.9% of the bleeding events in the on-demand treatment arm had successful outcomes following one injection of REBINYN. Thus, hemostatic efficacy of 40IU/kg for the treatment of minor and moderate bleeding was demonstrated in the on-demand treatment group.

#### 7.1.6 Other Endpoints

N/A

#### 7.1.7 Subpopulations

There were only 12 subjects less than 6 years of age and only 2 subjects over age 60. A subset of these subjects was in the on-demand arm. There is limited data for pediatric subjects in the on-demand group and those in the elderly population.

#### 7.1.8 Persistence of Efficacy

N/A

#### 7.1.9 Product-Product Interactions

N/A

#### 7.1.10 Additional Efficacy Issues/Analyses

N/A

#### 7.1.11 Efficacy Conclusions

The study drug was effective for on-demand use.

## 7.2 Indication #2

### Perioperative management

#### 7.2.1 Methods of Integration

Major surgery was primarily performed in Trial 3773 (the surgery trial). When Trial 3773 was closed, major surgery was then allowed in Trial 3775. The treatment regimen for major surgery was 1 pre-operative dose of 80 IU/kg REBINYN on the day of surgery, and dosing with 40 IU/kg in the postoperative period. During the postoperative period, dosing was at the investigator's discretion based on measured or expected FIX activity levels. It was recommended to treat with 2 doses of 40 IU/kg during the postoperative period from day 1 to 6.

Minor surgery was allowed in Trials 3747, 3775 and 3774. A dose of 40 IU/kg REBINYN prior to minor surgery was recommended to prevent perioperative bleeds. Fifteen minor surgeries were performed in Trial 3747. However, no data on the hemostatic effect during surgery was collected for these surgeries.

Efficacy of nonacog beta pegol during major surgery was investigated in Trial 3773. A total of 13 surgeries were performed in 13 subjects. Three surgeries were performed in 2 subjects in Trial 3775. Twenty minor surgeries were performed in Trial 3775, of which 17 were with 'excellent' hemostatic response, 1 was with 'good' hemostatic response, and 2 were not evaluated.

#### 7.2.2 Demographics and Baseline Characteristics

Please refer to Table 1 Baseline Demographics: Section 1.1 /Section 7.1.2 above. No significant differences in demographics or baseline characteristics were noted between the subjects who underwent surgery and the subjects who received on demand treatment. Subjects who underwent surgery in this trial included: thirteen subjects (18-70 years).

#### 7.2.3 Subject Disposition

Please refer to Section 6.2.10.1.3.

Out of the 13 subjects, six were new to the REBINYN clinical development program, two were transferred from the adult study, and 5 were transferred from the extension trial. There were no dropouts or discontinuations.

#### 7.2.4 Analysis of Primary Endpoint(s)

The primary endpoint in Trial 3773 was the hemostatic effect during surgery evaluated by the 4-point response scale as described previously. Effective hemostasis was confirmed in this trial.

#### 7.2.5 Analysis of Secondary Endpoint(s)

Secondary endpoint was the hemostatic effect of REBINYN when used for treatment of bleeds.

#### 7.2.6 Other Endpoints

N/A

#### 7.2.7 Subpopulations

N/A

#### 7.2.8 Persistence of Efficacy

Subjects received up to 4 injections of the study drug on post-op Days 1-6. On Post-Operative Days 7-13, they received up to 3 injections. Five subjects had additional doses Post-Operative Day 14 (2 subjects with 3 injections, 3 subjects with one injection).

#### 7.2.9 Product-Product Interactions

N/A

#### 7.2.10 Additional Efficacy Issues/Analyses

N/A

#### 7.2.11 Efficacy Conclusions

Hemostatic effect of REBINYN during surgery was confirmed. As per the primary endpoint, the success rate was 100% in 13 surgeries (9 major and 4 minor), 3 were judged to be 3 good and 10 were judged to be excellent. A pre-operative dose of 80 IU/kg dose of REBINYN was effective. The median number of additional 40 IU/kg doses in the post-operative period was 2.0 for Days 1 to 6, 1.5 for Days 7-13, and 3.0 for Days 1 to 13. The mean total consumption of REBINYN in the pre- and post-operative period was 241 IU/kg. There was no unexpected postoperative bleeding.

#### 7.3 Indication #3

Routine Prophylaxis

##### 7.3.1 Methods of Integration

Please see Section 6 above for key inclusion and exclusion criteria.

##### 7.3.2 Demographics and Baseline Characteristics

Please refer to Table 1 Baseline Demographics: Section 1.1 /Section 7.1.2 above. Subjects who were treated with routine prophylaxis included: 11 subjects (0-6 years); 11 subjects (7-12 years); 14 subject (13-17 years); 35 subjects (18-70 years).

##### 7.3.3 Subject Disposition

The two trials that evaluated routine prophylaxis include the adult and adolescent trial and pediatric trial. In Trial 3747, there were 30 subjects exposed in the 10 IU/kg prophylaxis group. Two subjects were withdrawn and 28 completed the trial. There were 29 subjects exposed in the 40 IU/kg prophylaxis group. Three subjects were withdrawn and 26 completed the trial. In Trial 3775, six subjects were withdrawn (two in the 10 IU/kg group and four in the 40 IU/kg group). In Trial 3774, five subjects were withdrawn.

##### 7.3.4 Analysis of Primary Endpoint(s)

The primary endpoint was a safety endpoint of immunogenicity. The primary endpoint in Trials 3747, 3775 and 3774 was incidence of inhibitory antibodies (inhibitors) against FIX. An inhibitor was defined as a titer  $\geq 0.6$  BU. No inhibitors were noted against FIX.

##### 7.3.5 Analysis of Secondary Endpoint(s)

Please refer to the efficacy results in Trial 3747. Subjects who completed Trial 3747 and continued into Trial 3775 had the opportunity to switch treatment regimen. Due to potential dose selection bias (subject or investigator could switch subject from one dose cohort), the data from Trial 3775 were not considered appropriate for pooling in the main efficacy evaluation of prophylaxis. These subjects in Trial 3775 changed arms are counted in duplicate in multiple treatment regimens.

40 IU/kg dose: This dose was used for on demand treatment of minor/moderate bleeds and also used as the routine prophylaxis dose. Subjects were randomized to the 40 IU/kg dose or the 10 IU/kg dose. The results demonstrated that the 40 IU/kg dose resulted in higher FIX levels as well as a lower ABR in comparison to the 10 IU/kg dose. Pediatric subjects were only given the 40 IU/kg dose prophylactically. There was an increase in estimated ABRs with increase in age. There were more joint bleeds in adolescent and adult subjects compared to pediatric subjects. This was expected as there is more joint disease in adults and a greater risk of experiencing bleeds. Hemostatic effect success rates were comparable for both adults and pediatric subjects for the 40 IU/kg dose.

#### 7.3.6 Other Endpoints

N/A

#### 7.3.7 Subpopulations

The median [IQR] ABR for all patients on 40 IU/kg once weekly prophylaxis from Trials 3747 and 3774 was 1.03 [0.00 ; 2.89]. (Table 3–12). The estimated bleeding rates increased slightly with age, ranging from 0.87 (95% CI: 0.26 ; 2.96) bleeds/patient year in age group 0–6 years up to 2.68 (95% CI: 1.51 ; 4.75) bleeds/patient year in the age group 18–70 years.

*Reviewer Comment: This is expected, as ABRs increase with age.*

#### 7.3.8 Persistence of Efficacy

N/A

#### 7.3.9 Product-Product Interactions

N/A

#### 7.3.10 Additional Efficacy Issues/Analyses

N/A

#### 7.3.11 Efficacy Conclusions

(b)(5) this indication is blocked by exclusivity by another FIX product until 2020.

*Reviewer Comment: Due to the potential neurocognitive function concerns raised by the nonclinical data, a plan for collection of postmarketing safety data will be requested under the IND and the data will need to be reviewed prior to approving this indication.*

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

Safety information collected included adverse events, laboratory assessments, physical examinations, vital signs, ECGs, and (in Study 3747 only) injection site tolerability.

The Case Report Forms for the initial visit provide examination findings for each organ system, including the neurological system. However, the physical exam findings during the initial visit do not include details of the type of tests performed (e.g., there is no



evidence of a comprehensive neurological exam or neurocognitive evaluation). Details of the physical exam findings for subsequent visits are not recorded by organ systems but targeted to identify any new findings judged by the investigator to be an undesirable adverse event. The safety monitoring plan in the REBINYN clinical study protocol did not include a comprehensive examination of the corresponding organ systems (e.g., neurocognitive testing; assessment of renal tubular dysfunction).

## 8.2 Safety Database

### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Five trials (Trials 3639, 3747, 3773, 3775 and 3774) have evaluated the clinical safety of REBINYN in previously treated male patients (PTPs) with severe or moderate hemophilia B (FIX activity <2%). A total of 115 PTPs have been exposed to the study drug.

### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In the completed trials, there has been a total of 8801 exposure days. The majority of the exposure to the study drug was observed in Trials 3747, 3774, and 3775.

Table 25: Duration of Exposure

Age (years)	Duration of exposure			
	0-1 year	1-2 years	2-3 years	>3 years
0-6 (n = 12)	1	0	1	10
7-12 (n = 13)	2	0	1	10
>12-17 (n = 18)	1	4	13	0
>17-60 (n = 70)	20	23	27	0
>60 (n = 2)	0	2	0	0

Source: Adapted from BLA125611/0 Summary of Clinical Safety Table1-3 page 21/341

### 8.2.3 Categorization of Adverse Events

All subjects dosed with the trial product were included in the safety analyses. The following were recorded: adverse events, serious adverse events, non-serious adverse events, and medical events of special interests.

### 8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

There are no concerns regarding pooling the data across the different studies as the study population was similar (PTPs with Hemophilia B), the endpoints of the trials were similar (safety endpoint of immunogenicity and efficacy endpoints of hemostatic effect). The demographics were similar in the trials.

## 8.4 Safety Results

### 8.4.1 Deaths

One subject died due to a fatal event of hepatocellular carcinoma. This was judged to not be related to the study drug.

#### 8.4.2 Nonfatal Serious Adverse Events

A total of 12 SAEs in 11 subjects were reported. One of the events was fatal (hepatocellular carcinoma, described above) and one event (skin ulcer) did not recover. All were judged to be likely not related except one event of hypersensitivity.

#### 8.4.3 Study Dropouts/Discontinuations

One subject was withdrawn from the extension study due to a fatal event of hepatocellular carcinoma. Two subjects were withdrawn due to ineffective therapy (one from the adult/adolescent trial and one from the extension trial). None of the subjects had inhibitors at any time point.

#### 8.4.4 Common Adverse Events

The most frequently reported adverse events were nasopharyngitis, upper respiratory tract infection, contusion, and cough.

#### 8.4.5 Clinical Test Results

As above.

#### 8.4.6 Systemic Adverse Events

N/A

#### 8.4.7 Local Reactogenicity

Four subjects reported to have local reactogenicity. One subject had injection site swelling, the second subject had injection site rash, the third had injection site/infusion site pain, and the fourth had injection site erythema. All injection site reactions resolved without sequelae and were judged to likely be due to the infusion of the study drug.

#### 8.4.8 Adverse Events of Special Interest

Fourteen medical events of special interest were reported.

Table 26: Adverse Events of Special Interest

Subject	Medical Event	Severity	Outcome
(b) (6)	Overdose	Mild	Recovered
	Pruritus	Mild	Recovered
	Subcutaneous injection	Mild	Recovered
	Medication error-reconstituted	Mild	Recovered
	wheezing	Mild	Recovered
	Overdose	Mild	Recovered
	Rash post sweating	Mild	Recovered
	Overdose	Mild	Recovered
	Overdose	Mild	Recovered
	Hypersensitivity	Severe	Withdrawn/Recovered
	Injection Site Rash	Mild	Recovered
	Incorrect Dose Administered	Mild	Recovered
	Overdose	Moderate	Recovered
	Overdose	Mild	Recovered

Source: Adapted from BLA125611/0 Summary of Clinical Safety Appendix I -page 211/341

There were 29 Nervous System AEs reported in 16 subjects from all three Phase 3 studies. The neurological symptoms included headache, dizziness, sciatic neuralgia, tongue biting, and speech disorder. The neurologic adverse events in the clinical trials are non-specific. Animals administered repeat doses of Rebinyn showed accumulation of PEG in the choroid plexus. The clinical implications of these findings in animals are unclear and whether patients may be vulnerable to neurologic/cognitive sequelae.

*Reviewer Comment: Definitive conclusions in this regard cannot be made as the studies were not designed to specifically evaluate neurocognitive function. It is unclear whether monitoring of neurologic function including neurocognitive assessments would be useful to mitigate any neurologic risks from REBINYN.. It is unclear whether monitoring of neurologic function including neurocognitive assessments would be useful to mitigate any neurologic risks from REBINYN*

Renal AEs were also of some concern as a result of the findings in animal studies. Therefore, renal AEs were also an area of focus during the review. Only 3 Renal AEs were reported in 2 subjects from all phase studies. There was a small decrease in mean estimated renal clearance in both adolescent/adults and pediatric subjects. Urinalysis was performed in the adolescent/adult trial, but was not performed in the pediatric trial. Three subjects tested positive for glucose at one time point; two of these subjects were positive only before dosing. The third subject was positive at the End of Treatment (EOT) visit. There were 27 subjects who tested positive for proteinuria; 12 tested positive prior to dosing with the study drug. There were 15 subjects who had positive test results for protein after dosing with REBINYN. Seven subjects had one positive test (1 at an intermediate visit and 6 at EOT). Six subjects had two positive tests (3 at baseline and EOT, 2 at an intermediate visit and EOT, 1 at baseline and an intermediate visit). One subject had three positive tests. One subject had 4 positive tests (all four visits).

A renal consult obtained stated that similar vacuoles have been seen in preclinical and clinical studies of other PEG products with a clinical signal for acute or chronic nephrotoxicity to date and there was no signal for acute or chronic nephrotoxicity based on the available data with REBINYN. The renal consult noted that the clinical database was small and limited to younger subjects with preserved renal function and nephrotoxicity would be more evident in a population at a higher risk. The consult concluded that monitoring of renal function was generally adequate and would not recommend additional clinical monitoring.

*Reviewer Comment: With the information from the renal consult, this clinical reviewer does not recommend additional pre-marketing studies to evaluate for PEG related renal tubular nephrotoxicity.*

## 8.5 Additional Safety Evaluations

### 8.5.1 Dose Dependency for Adverse Events

N/A

### 8.5.2 Time Dependency for Adverse Events

N/A

#### 8.5.3 Product-Demographic Interactions

N/A

#### 8.5.4 Product-Disease Interactions

N/A

#### 8.5.5 Product-Product Interactions

N/A

#### 8.5.6 Human Carcinogenicity

N/A

#### 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

#### 8.5.8 Immunogenicity (Safety)

A total of five subjects had positive titers for anti-CHO HCP antibodies. Anti-REBINYN binding antibodies were identified in three subjects, of which two were positive prior to exposure to REBINYN.

*Reviewer Comment: The observation of anti-REBINYN antibodies prior to receiving the drug may have been a lab error. It is unclear how this can occur. These antibodies observed did not have any clinical consequences.*

#### 8.5.9 Person-to-Person Transmission, Shedding

N/A

#### 8.6 Safety Conclusions

A total of 647 Adverse Events (AEs) was reported in 98 (85.2%) subjects. The most common adverse events were nasopharyngitis (35 events in 19 [16.5%] subjects), upper respiratory tract infection (20 events in 13 [11.3%] subjects), contusion (27 events in 15 [13.0%] subjects) and cough (24 events in 15 [13.0%] subjects).

There were 29 Nervous System AEs reported in 16 subjects from all three Phase 3 studies. The neurological symptoms included headache, dizziness, sciatic neuralgia, tongue biting, and speech disorder. The neurologic adverse events in the clinical trials are non-specific. Of particular concern may be the use of REBINYN in infants and children who have developing brains, and the use of REBINYN in patients who are cognitively impaired as well as the elderly. Factors such as duration of use, cumulative dose, age of the patient, and related comorbidities may increase the neurologic risks to patients exposed to REBINYN; however, definitive conclusions in this regard cannot be made as the studies were not designed to specifically evaluate neurocognitive function. However, it is unclear whether the clinical monitoring of renal function was adequate to detect all clinically important renal signs or symptoms. The clinical trials did not find any safety signal that was clearly likely to be caused by PEG accumulation. No subject had an inhibitor or thromboembolic event.

The reviewer recommends the information regarding the potential for neurocognitive impairments is included in the Warnings and Precautions of the label. The potential risks of neurocognitive impairment are considered clinically significant and especially relevant to any future indication of routine prophylaxis. The bases for these potential risks result

from the observation of PEG accumulation in the choroid plexus in the animal studies and the role of the choroid plexus on the neurological function and brain development. These recommendations are consistent with the FDA's current thinking as noted in the "Guidance for the Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labelling for Human Prescription Drugs and Biological Products – Content and Format."

## 9. ADDITIONAL CLINICAL ISSUES

### 9.1 Special Populations

N/A

#### 9.1.1 Human Reproduction and Pregnancy Data

N/A

#### 9.1.2 Use During Lactation

N/A

#### 9.1.3 Pediatric Use and PREA Considerations

REBINYN triggered PREA for the on demand and perioperative management indication. The routine prophylaxis indication was orphan designated.

The Pediatric Review Committee concurred with the pediatric assessment (including all pediatric age groups) for this BLA.

#### 9.1.4 Immunocompromised Subjects

N/A

#### 9.1.5 Geriatric Use

N/A

### 9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

## 10. CONCLUSIONS

The completed studies showed overall efficacy with REBINYN in all age groups. The data from the adult and pediatric subjects continue to show an ABR in line with the appropriate range noted for hemophilia B products. The surgery study shows efficacy in this cohort of subjects. There were no reports of any cluster of adverse events identified. There were no reports of inhibitory antibodies to REBINYN. However, due to the preclinical findings of PEG accumulation and vacuolation, there is an unknown risk to subjects exposed to REBINYN for chronic use. Moreover, lifelong use of REBINYN warrants further exploration to detect any clinical safety signals. The clinical trial results support the safety and efficacy of REBINYN for on-demand and perioperative treatment of hemophilia B.

## 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

### 11.1 Risk-Benefit Considerations

#### Benefit Considerations

- On-demand REBINYN is effective for treatment of, and prevention of, spontaneous or traumatic bleeding in patients with Hemophilia B.
- REBINYN is effective in the perioperative setting for reduction of bleeding during surgery.

#### Risk Considerations

- Per the pre-clinical studies, the choroid plexus developed PEG accumulation and vacuolation. The neurological monitoring during the clinical trials may have been insufficient to detect early signs of dysfunction in these systems.
- In the absence of pre-clinical data to confirm the reversibility of the pathological findings and the duration of monitoring necessary to assess the long-term risks of PEG accumulation, and vacuolation, in the target tissues, the adequacy of the safety monitoring period in the clinical studies is unclear.
- If PEG accumulation, and vacuolation, were to occur in humans, then the developing neurological system may be at the greatest risk for associated adverse events. Therefore, the most vulnerable population may be pediatric subjects and geriatric subjects with cognitive impairment.
- The long-term effects of PEG accumulation, and vacuolation, are unknown in the elderly population, who may be particularly susceptible to renal dysfunction and cognitive impairment. The median age in Study 3747 for subjects receiving 40 IU/kg (routine prophylaxis in adults and adolescents) was 26 years. Only two subjects at least age 60 years (i.e., one subject age 60 and one subject age 65 years) were included in the study; therefore, there is a paucity of data on REBINYN use in older adults.
- The duration of administration of the prophylactic regimen was 52 weeks in Study 3747. Therefore, there are few data on the safety of REBINYN when administered for longer periods, as would be expected if the product is used for chronic prophylaxis.
- Although no reports of inhibitory antibodies to REBINYN were noted in Studies 3747, 3773 and 3774, these antibodies have been reported as part of the IND safety reporting in the ongoing study in previously untreated patients (PUPs). The quantification of the risks in PUPs will be completed after completion of this study. The risks from inhibitory antibodies are expected as with the class of recombinant FIX products for treatment of Hemophilia B.
- Overall, there were no serious adverse events related to REBINYN. The risks for development of inhibitory antibodies are considered an expected adverse event. The potential for neurologic risks from REBINYN were considered when making the recommendation in favor of a marketing approval for REBINYN for short-term use. Clinical judgment was exercised due to the paucity of safety data to assess this neurological risk, when making a recommendation to support a marketing approval of REBINYN for short-term use. These clinical considerations included a) the lower risk for PEG accumulation given the short term use in both pediatric and adult

patients and b) the recommendations with regard to short-term use from the members of the Advisory Committee. In addition, given the uncertainties of neurological risks with long-term use, the prescribing information for REBINYN includes a limitation of use statement related to routine prophylaxis and neurological considerations for chronic use and use in pediatric and geriatric age groups.

#### Available Therapies for Hemophilia B

- Of the recombinant FDA-approved Factor IX products, two products are administered weekly for use in adults and children. These products are also approved for treatment of peri-operative and acute bleeding.

Table 27: Benefit Risk

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>Hemophilia B is a rare condition with variable deficiency of coagulation factor IX.</li> <li>Hemophilia is accompanied by bleeding into tissues and joints which can be spontaneous, post-traumatic, or perioperative.</li> <li>Bleeding can be acutely devastating, such as intracranial bleeding, or chronically destructive such as hemophilic arthropathy.</li> </ul>	<ul style="list-style-type: none"> <li>Hemophilia B is a serious, progressive, life-threatening disease.</li> <li>The bleeding associated with hemophilia can cause clinically significant complications.</li> <li>Current treatment is expensive and carries risks of infection or adverse reactions.</li> </ul>
<b>Unmet Medical Need</b>	<ul style="list-style-type: none"> <li>There are two other long acting recombinant factor IX products licensed for use by FDA.</li> <li>Other plasma-derived factor IX products exist, but carry the same risks as other human plasma products, such as acute hypersensitivity reactions and immunogenicity.</li> </ul>	<ul style="list-style-type: none"> <li>Although alternative recombinant therapy exists for Hemophilia B, it is expensive and even higher costs for those on prophylactic therapy. Increasing the number of available licensed products could have a positive impact and allow options for hemophilia subjects who remain untreated due to high costs.</li> </ul>
<b>Clinical Benefit</b>	<ul style="list-style-type: none"> <li>REBINYN was shown to be effective for treatment of, and prevention against spontaneous or traumatic bleeding by both prophylactic or on-demand regimens</li> <li>REBINYN was shown to be effective in the perioperative setting for reduction of bleeding during surgery.</li> </ul>	<ul style="list-style-type: none"> <li>REBINYN is similarly effective to the currently licensed recombinant products.</li> </ul>
<b>Risk</b>	<ul style="list-style-type: none"> <li>The most substantial risks with REBINYN are an unknown safety risk, particularly to the neurologic system as evidenced by the animal data, with chronic exposure.</li> <li>No safety signals were apparent in the subjects treated in the trials, although there is paucity in data for the most vulnerable populations (pediatric and elderly).</li> </ul>	<ul style="list-style-type: none"> <li>The risk of long-term exposure to FIX products is the development of inhibitory antibodies.</li> <li>There is an unknown safety risk with chronic exposure.</li> </ul>
<b>Risk Management</b>	<ul style="list-style-type: none"> <li>An approval is recommended for the perioperative and on-demand indication.</li> <li>The risks related to chronic exposure in all ages preclude a recommendation for marketing approval in the routine prophylaxis indication and labeling information regarding chronic use is recommended.</li> </ul>	<ul style="list-style-type: none"> <li>The clinical reviewer recommends additional pre-marketing studies in all age groups to evaluate the safety of routine prophylaxis and related to the PEG accumulation in the choroid plexus as noted in the pre-clinical studies. Such studies should incorporate neurocognitive assessments as part of the clinical monitoring.</li> </ul>



### 11.2 Risk-Benefit Summary and Assessment

There are no clinical issues with the efficacy for REBINYN. Two other long-acting drugs are available with once weekly dosing and similar ABRs. The clinical trials were not designed to investigate the possible clinical effects of PEG accumulation/vacuolation. No clear safety signal from accumulation of PEGylation was observed in the clinical trials. It is not clear what the actual clinical impact is at this time. Moreover, it is unclear whether the monitoring of neurologic function was adequate to detect all clinically important neurologic signs or symptoms as the clinical studies were not specifically designed to assess neurocognitive function. In addition, it is unclear whether the size of the safety database (i.e., number of adult and/or pediatric subjects exposed to the product; duration of follow-up of those subjects) is sufficient to assess the safety of the product. The pediatric and elderly population is most vulnerable to the potential effects of chronic administration. It is unclear whether monitoring of neurologic function including neurocognitive assessments would be useful to mitigate any neurologic risks from REBINYN. This aligns with opinions of the experts in the Advisory Committee.

Overall, the benefit/risk profile for the use of REBINYN for on-demand treatment and perioperative management of Hemophilia B is favorable.

### 11.3 Discussion of Regulatory Options

The available data support approval of the indication for on-demand treatment and perioperative management.

The indication for routine prophylaxis is blocked by exclusivity by another product until 2020 and will not be approved in this BLA. Furthermore, evaluation of the potential risks of neurocognitive sequelae for routine prophylaxis needs to be considered. Due to the safety concerns, a discussion with the Office of Biostatistics and Epidemiology was held to inquire about a plan and recommendations regarding postmarketing safety data to be collected and reviewed prior to consideration to approve this indication. Per their recommendation, a PMR for routine prophylaxis cannot be required as this indication is not being approved. OBE does not recommend a PMC at this time. However, the clinical team recommends that it may be beneficial to collect safety data from the approved indications. The applicant would be able to submit this data to the IND and based upon this data submit an efficacy supplement for the indication of routine prophylaxis for review.

### 11.4 Recommendations on Regulatory Actions

An approval for the on demand treatment and perioperative management indication is recommended.

The routine prophylaxis indication will not be approved.

### 11.5 Labeling Review and Recommendations

The revised package insert (PI) was reviewed, commented, and/or revised by the appropriate discipline reviewers. APLB conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

### 11.6 Recommendations on Postmarketing Actions

N/A

