Application Type	Original BLA
STN	125671/0
CBER Received Date	February 27, 2018
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Division / Office	OTAT
Committee Chair	Andrey Sarafanov, Ph.D.
Clinical Reviewer(s)	Najat Bouchkouj, M.D.
Project Manager	Jean Dehdashti, M.Sc., RAC
Reviewer Name(s)	Lin Huo, Ph.D.
Supervisory Concurrence	Boguang Zhen, Ph.D., Branch Chief, Therapeutics Evaluation Branch
	John Scott, Ph.D., Director, Division of Biostatistics
Applicant	Novo Nordisk, Inc.
Established Name	Turoctocog alfa pegol (N8-GP)
(Proposed) Trade Name	ESPEROCT
Pharmacologic Class	Recombinant human factor VIII, pegylated
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for Injectable Solution / Intravenous
Dosing Regimen	Adults and adolescent (≥ 12 years): 50 IU/kg every 4 days. Children (<12 years): (b) (4) IU/kg twice weekly A regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes.
Indication(s) and Intended Population(s)	For use in adults and children with hemophilia A for: on-demand treatment and control of bleeding episodes; perioperative management; and routine prophylaxis

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GLOSSARY

ABR	Annualized Bleeding Rate
AE	Adverse Event
BLA	Biologics License Application
BMI	Body Mass Index
BU	Bethesda Unit
BW	Body Weight
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CSR	Clinical Study Report
ED	Exposure Day
EMA	European Medicines Agency
EOT	End of Trial
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug
IU	International Unit
IV	Intravenous
kDa	Kilodalton
LOCF	Last Observation Carried Forward
PEG	Polyethylene Glycol
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PTPs	Previously Treated Patients
rFVIII	Recombinant human factor VIII
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal Half-life
UK	United Kingdom
US	United States
WFH	World Federation of Hemophilia

1. EXECUTIVE SUMMARY

This is an original Biologics License Application (BLA) for the applicant's purified recombinant human factor VIII (rFVIII) product ESPEROCT (also referred as N8-GP in this memo) with a 40 kDa PEG conjugated to the protein. The PEG is attached to the O-linked glycan in the truncated B-domain of rFVIII (turoctocog alfa). The PEGylation increases the half-life of the protein.

ESPEROCT is proposed for the indication of on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in previously treated adults and children with hemophilia A.

The efficacy of ESPEROCT for prophylaxis and treatment of bleeds was evaluated in adolescents and adults in trial NN7088-3859 and in children in trial NN7088-3885. The efficacy of N8-GP for perioperative management was evaluated in trial NN7088-3860.

Trial NN7088-3859 included 186 subjects, 161 adults (18 to 65 years old) and 25 adolescents (12 to <18 years old); it consisted of a Main Phase and two Extension Phases. The Main Phase and Extension 1 are complete and Extension 2 is still ongoing at the time of the submission.

During the **Main Phase**, 175 subjects received the prophylaxis regimen which consisted of 50 IU every 4 days (q4D), while 12 adults chose to be treated on-demand. A total of 165 subjects (91%) completed the Main Phase of this trial.

The co-primary endpoints in the Main Phase are the incidence rate of FVIII-inhibitor (≥ 0.6 Bethesda Units [BU]) and Annualized Bleeding Rate [ABR] for subjects receiving prophylaxis treatment. One adolescent subject developed FVIII inhibitors which resulted in an estimated inhibitor rate of 0.6% and a one-sided 97.5% upper confidence limit for the inhibitor rate of 3.8%. As this is below the pre-specified limit of 6.8 %, this co-primary endpoint was met. The ABR was estimated by Poisson regression model allowing for over-dispersion and imputed for subjects who withdrew prematurely in the primary analysis. The estimated ABR in the prophylaxis arm was 3.70 (95% CI: 2.94; 4.66). The mean ABR was 3.73 (SD: 5.90). The median ABR was 1.33 (IQR: 0.00; 4.61). These estimates are consistent with other FVIII products. Out of the 968 bleeding episodes in the trial, 964 bleeds were rated. The treatment response was assessed as "good" or "excellent" in 88.4% of all rated bleeds.

Extension 1 compared two dose regimens: 75 IU/kg every 7 days (q7D) and 50 IU/kg q4D. Of the 150 subjects who continued into Extension 1, 55 subjects chose to be randomized (2:1) to 75 IU/kg q7D (38 subjects) and 50 IU/kg q4D (17 subjects).

The Poisson-estimated mean ABR in the q7D prophylaxis arm was 3.57 (95% CI: 2.13; 6.00). The raw mean ABR was 3.59 (SD: 6.62). The median ABR was 0.00 (IQR: 0.00; 2.36). Subjects randomized to q4D with 50 IU/kg had a Poisson-estimated mean ABR of 1.77 (95% CI: 0.59; 5.32). The raw mean ABR was 1.77 (SD: 2.42). The median ABR was 0 (IQR: 0.00; 2.23). Out of the 1436 bleeding episodes in the Main Phase and Extension 1 of the trial, 1420 bleeds were rated. The

treatment response was assessed as "good" or "excellent" in 87.7% of all rated bleeds.

During the Main Phase and two Extensions of the trial, one death occurred in a 67-year-old subject which was considered unlikely related to ESPEROCT. A total of 49 SAEs were recorded in 31 (16.7%) subjects. Two of these events were evaluated as possibly and probably related to trial product.

Trial NN7088-3860 included 33 previously treated adolescents/ adults who underwent 45 major surgeries.

The procedures included 15 joint replacements, 9 arthroscopic orthopaedic interventions, 17 other orthopaedic interventions, and 4 non-orthopaedic surgeries. The haemostatic effect of ESPEROCT was rated as "excellent" or "good" in 43 of 45 surgeries (95.6%), while the effect was rated as "moderate" in 2 surgeries (4.4%).

A total of 5 serious adverse events were reported in 4 surgeries. Two of the serious adverse events were judged by the investigator as possibly related to trial product. There were no deaths in the trial.

Trial NN7088-3885 included 68 subjects who were evenly divided with 34 in each age group, 0–<6 and 6–<12 years of age. All subjects received the same prophylaxis regimen of approximately 60 IU/kg (50–75 IU/kg) twice weekly. The Main Phase is complete and the Extension is still ongoing at the time of the submission.

The primary endpoint of the trial was incidence of inhibitory antibodies against FVIII ≥0.6 BU during the Main Phase of the trial. No FVIII inhibitors were observed.

Out of the 70 bleeding episodes in the **Main Phase**, 67 bleeds were rated. The treatment response was assessed as "good" or "excellent" in 78.6% of all bleeds. The estimated ABR was 3.29 (95% CI :2.16; 5.01), 4.28 (95% CI :2.66; 6.89) in the 0-5 year age-group, and 2.30 (95% CI :1.20; 4.40) in the 6-11 year age-group. The median ABR was 1.95 (IQR: 0.00; 2.79) and comparable between the two age-groups. The mean ABR was 3.87 (SD: 9.68) for the 0-5 age group and 2.29 (SD: 2.86) for the 6-11 age group.

A total of 17 SAEs were reported in 15 (22.1%) of the subjects, of which 2 SAEs were evaluated as probably related to trial product. There were no deaths in the trial.

Conclusion and Recommendation:
All the primary efficacy endpoints and the key secondary endpoints in the above three trials were reviewed and verified. No discrepancies were found. However, given the number of subjects who required rescue treatment and change to a more frequent dosing and the higher ABR in the q7D prophylaxis regimen, I do not recommend including this dosing regimen in the label due to the increased risk of bleeding under this regimen. Other than this, the statistical evidence supports approval of the applicant's proposed indications for ESPEROCT in BLA 125671/0.

2. CLINICAL AND REGULATORY BACKGROUND

ESPEROCT is a novel rFVIII product based on the currently licensed Novoeight® (turoctocog alfa) with an extended half-life due to the covalent conjugation of a 40 kDa polyethylene glycol (PEG) moiety to an O-linked glycan site on the B-domain of turoctocog alfa. The mechanism of action for ESPEROCT is based on replacement of

the deficient or absent FVIII in patients with hemophilia A. ESPEROCT is supplied as lyophilized powder in sterile glass vials and is reconstituted with (b) (4) of 0.9% sodium chloride (NaCl) for IV injection. It will be available in five single-use vial sizes of 500 IU, 1000 IU, 1500IU, 2000 IU, and 3000 IU.

2.1 Disease or Health-Related Condition(s) Studied

Prevalence

Hemophilia A is considered an orphan disease with approximately 400,000 patients worldwide. It is caused by an absence or low levels of the coagulation protein FVIII. It is a lifelong X- linked disorder (the gene for FVIII is located on the X-chromosome), affecting almost exclusively males. It affects about 1 in 5000 live male births. In the United States, the mean prevalence is approximately 8 per 100,000 male individuals (Stonebraker et al. 2010).

Clinical presentation

Hemophilia A is usually diagnosed by measuring FVIII clotting activity (FVIII:C) level in the plasma of a patient. There is a direct correlation between FVIII activity levels and clinical manifestations. Hemophilia A is defined as severe if the plasma FVIII:C level (measured as IU/dL) is <1%, moderate if it is between 1% and 5%, and mild if it is between > 5% and 40% of normal.

Hemophilia A can result in spontaneous and life-threatening bleeding events or excessive bleeding in response to trauma. Bleeds occur in muscle, organs, soft tissue and most frequently in joints, which leads to joint damage and severe disability, with major effects on the physical, psychosocial, quality of life, and financial conditions of the hemophilia patients.

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

Standard treatment for these patients is the replacement of the missing protein by intravenous infusion of either plasma-derived FVIII or rFVIII. This increases the plasma concentrations of FVIII, thereby enabling a temporary correction of the factor deficiency and reversal of the bleeding tendencies. Until recently, the treatment regimens have been either **on-demand** therapy (given when a bleed occurs) or **prophylaxis** (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). Products with an extended $t_{1/2}$ and less frequent infusion requirement have been approved recently in the US, Canada, Europe, Australia, and other countries worldwide (such as Elocta®, Eloctate®, Adynovate®) which provide new treatment options with dosing intervals of 3 to 5 days.

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

At present, ESPEROCT is neither approved for marketing nor withdrawn or suspended from marketing authorization worldwide.

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

FDA had multiple interactions with the applicant throughout the IND and BLA process. Pre-IND meeting was held in April 2019 and IND was initiated in July 2010. End of phase 2 meeting was held in August 2011 and a type C meeting was held in February 2017 to discuss the Applicant's plan for converting the clinical study data

from legacy format to CDISC- compliant format. Pre-BLA meeting was held in December 2017 and discussion included the BLA content/format and timing for the submission.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

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

5.1 Review Strategy

The efficacy of ESPEROCT in previously treated patients with severe hemophilia A was evaluated in three trials (trials NN7088-3859, NN7088-3885, and NN7088-3860). The efficacy of ESPEROCT for prophylaxis and treatment of bleeds was evaluated in adolescents and adults in trial NN7088-3859 and in children in trial NN7088-3885. The efficacy of ESPEROCT for perioperative management was evaluated in trial NN7088-3860.

All three trials are reviewed individually in section 6. Trial NN7088-3859 consisted of a Main Phase followed by two Extension Phases. The completed Main Phase and Extension 1 (also referred to as Extension Phase part 1) are reviewed for the efficacy results in this memo. The on-going Extension 2 (also referred to as Extension Phase part 2) was reviewed together with the Main Phase and Extension 1 for safety results but the efficacy results are not included in this memo. Trial NN7088-3885 consisted of a main and an Extension Phase. The completed Main Phase is reviewed for the efficacy results in this memo. The on-going Extension Phase was reviewed together with the Main Phase for the safety results but the efficacy results are not included in this memo.

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

- Original submission under BLA 125671/0
  - Module 1.6: Meetings
  - Module 1.14: Labeling
  - Module 2.2: Introduction
  - Module 2.5: Clinical Overview
  - Module 2.7: Clinical Summary
  - Module 5.3.5.2: CSR for NN7088-3859, SAPs and tabulation data
    - The main CSR (1561 pages), Version 1.0, dated December 17, 2014 with 167-page main text.
    - The main Protocol (296 pages), Amendment 18, dated November 29, 2013.
    - The main SAP (46 pages), Version 0.1, dated December 17, 2014.
    - The Extension part 1 CSR (2761 pages), Version 1.0, dated April 24, 2017 with 173-page main text.
    - The Extension part 1 Protocol (296 pages), Amendment 18, dated May 15, 2016.
    - The Extension part 1 SAP (68 pages), Version 1.0, dated May 15, 2016.
    - The Extension part 2 CSR (2371 pages), Version 1.0, dated December 4, 2017 with 155-page main text.

        - The Extension part 2 Protocol (301 pages), Amendment 19, dated December 4, 2017.
        - The Extension part 2 SAP (25 pages), Version 2.0, dated October 2, 2017.
    - Module 5.3.5.2: CSR for NN7088-3860, and tabulation data
        - The main CSR (711 pages), Version 1.0, dated December 4, 2017 with 108-page main text.
        - The main Protocol (137 pages), Amendment 5, dated November 30, 2017.
    - Module 5.3.5.2: CSR for NN7088-3885, and tabulation data
        - The main CSR (830 pages), Version 1.0, dated December November 23, 2015 with 135-page main text.
        - The main Protocol (156 pages), Amendment 3, dated November 13, 2015.
        - The Extension part CSR (1153 pages), Version 1.0, dated November 6, 2017 with 126-page main text.
        - The Extension part Protocol (162 pages), Amendment 5, dated November 6, 2017.
        - The Extension part SAP (15 pages), Version 1.0, dated August 30, 2017.

- BLA amendment 125671/16, Module 1.11.3, Response to FDA information request dated July 13, 2018.
- BLA amendment 125661/49, Module 1.11.3, Response to FDA information request dated December 11, 2018
- BLA amendment 125671/53, Module 1.11.3, Response to FDA information request dated December 13, 16 and 17, 2018
- BLA amendment 125661/56, Module 1.11.3, Response to FDA information request dated December 13, 16 and 17, 2018

5.3 Table of Studies/Clinical Trials

The clinical development program of N8-GP consists of six studies. An overview of these studies is provided in Table 1. Only three studies (NN7088-3859, NN7088-3860, and NN7088-3885) which evaluated efficacy of N8-GP are reviewed in this memo.

Table 1. Overview of N8-GP Clinical Studies

Trial ID/ Status	Trial design	N8-GP dose and treatment regimen[a]	Number of patients[b] (age range)
Previously treated patients			
Trial 3776: Completed	*First human dose trial* Open-label, dose escalation	*Single-dose PK*: 25, 50, 75 IU/kg	Total: 26 patients (20–60 years)
Trial 3859 Pivotal part of the trial (Interim report): Completed	*Pivotal trial* Open-label, non-controlled	Main phase: *Prophylaxis*: 50 IU/kg Q3–4D *Treatment of bleeds*: 20–75 IU/kg *Single-dose PK*: 50 IU/kg	Total: 186 patients (12–66 years) PK: 24 patients
Extension phase part 1 (Interim report): Completed		Extension phase part 1: *Prophylaxis*: 50 IU/kg Q3–4D or 75 IU/kg Q7D *Treatment of bleeds*: 20–75 IU/kg	Total: 150 patients (12–66 years)
Extension phase part 2 (Interim report): Ongoing		Extension phase part 2: *Prophylaxis*: 50 IU/kg Q3–4D or 75 IU/kg Q7D *Treatment of bleeds*: 20–75 IU/kg	Total: 139 patients (12–66 years)
Trial 3860 (Interim report): Ongoing	*Surgery trial* Open-label, non-controlled	*Pre-surgery period*: Preoperative dose aiming for a FVIII activity level of 80-100%. *Post-operative period* *Days 1–6*: At the investigator's discretion, aiming for a FVIII activity level above 50%. *Days 7–14*: At the investigator's discretion.	Total: 34 patients; 45 surgeries (15–69 years)
Trial 3885 Main phase (Interim report): Completed Extension phase (Interim report): Ongoing	*Paediatric trial* Open-label, non-controlled	*Prophylaxis*: ~60 IU/kg (50–75) twice-weekly with adjustment to every third day if necessary* *Treatment of bleeds*: 20–75 IU/kg *Single-dose PK*: 50 IU/kg	Total: 68 patients (1–11 years) PK: 27 patients
Trial 4033: Completed	*Pharmacokinetics & safety of N8-GP from the pivotal and the commercial process* Randomised, double-blind, cross-over	*Single-dose PK*: 50 IU/kg	Total: 21 patients (20–71 years)
Previously untreated patients			
Trial 3908 Ongoing	*Previously untreated patients* Open-label, non-controlled	*Prophylaxis:* 50–75 IU/kg every third day, twice weekly or every seventh day. *Treatment of bleeds*: 20–75 IU/kg	32 patients (planned 125 patients <6 years of age)

PK: pharmacokinetics; Q3–4D: patients starting dose was every fourth day, subsequently patients could switch to twice-weekly*; Q7D: every seventh day dosing.

*Dosing frequency could be adjusted at the discretion of the investigator based on patient response.

[a] Bleeds were treated according to the severity and location of the bleed. Additional doses for treatment of a bleed could be given at the investigator's discretion. [b] Number of exposed patients shown; all patients had severe haemophilia A with FVIII activity <1%.

Source BLA 125671/0; Module 2.5 Clinical overview, Table 1-2.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 NN7088-3859

NN7088-3859 study was titled "A Multi-National Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Hemophilia A". The trial consisted of a Main Phase followed by two Extension Phases. Main Phase is considered pivotal part of the study. Both Main Phase and Extension 1 are complete. Extension 2 is still on-going at the time of the BLA submission.

6.1.1 Objectives (Primary, Secondary, etc.)

Main Phase

Co-Primary objective:

- To evaluate the immunogenicity of N8-GP in previously treated subjects with hemophilia A
- To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeds during prophylaxis)

Secondary objectives:

- To evaluate the clinical efficacy of N8-GP when treating bleeds in subjects with hemophilia A
- To evaluate the safety of N8-GP when used for prevention of bleeds and treatment of bleeds in subjects with hemophilia A
- To evaluate PK properties of N8-GP
- To evaluate patient reported outcomes (PRO)
- To evaluate the health economic impact of N8-GP treatment
- Generation of a population-based PK-model for N8-GP

Extension 1

- To investigate the safety and efficacy of every 7-day dosing by evaluating ABR for this dosing regimen

Extension 2

- To assess long-term safety and efficacy of N8-GP

6.1.2 Design Overview

Trial NN7088-3859 was a multi-national, multi-center, open-label, non-controlled trial evaluating the efficacy of N8-GP for prophylaxis and treatment of bleeds in adolescent and adult subjects with severe hemophilia A aged 12−66 years. Subjects were required to have at least 150 exposure days to a previous FVIII product to be included in the trial. This trial consisted of a Main Phase followed by two Extension Phases.

Main Phase

In the Main Phase, there were two treatment groups: on-demand and prophylaxis. Treatment was non-randomized and based on the choice of the subject and investigator at the screening visit. Subjects in the prophylaxis arm received a 50 IU/kg dose of N8-GP every four days (referred to as q4D), in most cases administered by the subject at home. Subsequently, the dosing interval for prophylaxis could be shortened to twice-weekly if deemed necessary by the investigator. The subjects in the on-demand arm could switch to prophylaxis after 6 months of treatment if the

prophylaxis arm was still open for enrolment. A minimum of 155 subjects had to complete the trial, including at least 10 subjects in the on-demand group.

All bleeds were to be treated as soon as they were identified with doses of N8-GP between 20−75 IU/kg according to the severity and location of the bleed. If major surgery was required, subjects could transfer to the surgery trial (trial NN7088-3860) and return back to trial NN7088-3859 after surgery was complete.

The end of the Main Phase depended on when the last subject had at least 50 EDs or approval of the Extension Phase in country. Those subjects choosing to continue in the trial were transferred into the Extension Phase at the end of the Main Phase. The duration of the Main Phase was approximately 1 year.

Extension 1
Subjects transferring from the Main Phase into Extension 1 were enrolled on the same day as the end of the Main Phase. For each subject, the duration of Extension 1 was 6 months.

Subjects on prophylaxis with 0−2 bleeds during the last 6 months of the Main Phase had the option of being randomized (2:1) to N8-GP 75 IU/kg every 7 days (q7D hereafter) or 50 IU/kg q4D in Extension 1. Subjects with 3 or more bleeds within the last 6 months of the Main Phase and subjects with low bleeding rates who were unwilling to be randomized continued on q4D dosing. These subjects comprised the non-randomized subject group. Subjects randomized to q7D who met one of the following criteria over an eight-week period had to switch back to q4D dosing (non-randomized group): two spontaneous bleeds or one severe bleed requiring hospitalization.

Subjects who were treated on-demand throughout the Main Phase were to continue with the on-demand regimen in the Extension Phase.

All bleeds during the Extension Phase were treated with N8-GP as in the Main Phase, with doses between 20−75 IU/kg according to the severity and location of the bleed. As in the Main Phase, subjects could undergo minor surgery and remain in the trial or transfer to the surgery trial if major surgery was required.

Extension 2
Subjects entering Extension 2 were to continue to receive either prophylaxis or on-demand treatment according to the treatment they received in part 1. However, in Extension 2, subjects receiving prophylaxis treatment could switch between q3−4D and q7D at the discretion of the Investigator.

6.1.3 Population

Key subject eligibility criteria:

- Male subjects with severe congenital hemophilia A (FVIII activity <1%)
- Documented history of at least 150 exposure days to other FVIII products
- Age ≥12 years and body weight ≥35 kg (or male ≥18 years of age in countries where enrollment of minors was not permitted)
- BMI ≤ 35

6.1.4 Study Treatments

Main Phase

For an overview of the treatments in the Main Phase of the trial, please see Table 1.

Table 1 Overview of treatments

	Treatment	Dose	Frequency
Main Phase	Prophylaxis	50 IU/kg BW	Every 4th day/Twice weekly
	Treatment of bleeds	20-75 IU/kg BW	Investigator's discretion

Source: Adapted from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase CSR, Table 9-1.

Extension 1

The prophylaxis dose of N8-GP was administered in the non-randomized group every 4 days or in the randomized group every 4 day (50 IU/kg of N8-GP) or every 7 day (75 IU/kg of N8-GP) depending on which treatment arm the subject was allocated to. Based on the bleeding pattern, the Investigator could change the every 7 day prophylaxis treatment to an every 4 day treatment regimen (the non-randomized arm) at any time. Changing vice versa was not permitted.

6.1.6 Sites and Centers

The trail was conducted at 77 sites in 22 countries, as follows: Australia (3 sites); Brazil (1 site); Croatia (1 site); Denmark (2 sites); France (3 sites); Germany (5 sites); Hungary (2 sites); Israel (1 site); Italy (2 sites); Japan (8 sites); Malaysia (2 sites); Netherlands (2 sites); Norway (1 site); Russia (1 site); South Korea (1 site); Spain (2 sites); Sweden (1 site); Switzerland (3 sites); Taiwan (2 sites); Turkey (3 sites); UK (6 sites); US (25 sites).

6.1.8 Endpoints and Criteria for Study Success

Main Phase

Co-primary endpoints:

- The incidence rate of FVIII-inhibitors ≥ 0.6 BU
- ABR for subjects receiving prophylaxis treatment

Confirmatory secondary efficacy endpoints:

- The hemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for hemostatic response (excellent, good, moderate and non) by counting excellent and good as success and moderate and none as failure.
  The following definitions for response to treatment were suggested:
  Excellent: abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion;
  Good: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than one infusion for complete resolution;
  Moderate: probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than one infusion;
  None: no improvement or worsening of symptoms.

Additional supportive efficacy endpoints:

- Consumption of N8-GP (number of injections and IU/kg) per bleed
- Consumption of N8-GP (number of injections and IU/kg per month and per year) during prophylaxis and on-demand treatment

- Hemostatic effect as measured by recovery and trough levels FVIII:C (in all subjects receiving prophylaxis treatment)
- Patient Reported Outcomes and Health Economic Endpoints

Safety endpoints:

- AEs and SAEs reported during the trial
- Changes in vital signs (blood pressure, pulse, temperature, respiratory rate)

Extension 1

- ABR for subjects receiving q7D 75 IU/kg prophylaxis treatment
- AEs in q7D 75 IU/kg prophylaxis subjects

In addition, the co-primary and secondary endpoints described above in the Main Phase will be evaluated again in Extension 1 based on compiled data from the Main Phase and the Extension 1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations

- **Full analysis set (FAS)** –The full analysis set consisted of all subjects exposed to N8-GP in this trial. The efficacy analyses were based on the FAS and all available information until end of trial (EOT) visit.
- **Safety analysis set (SAS)** – The safety analysis set consisted of all subjects exposed to N8-GP in this trial. The analyses of the safety endpoints were based on the safety analysis set and all available information until EOT visit.

FAS and SAS are identical in the Main Phase, Extension 1 of the trial.

Subgroup analyses

The subgroup analyses planned for ABR and the hemostatic response with prophylaxis treatment included:

- Age group (<18 years, >=18 years)
- Race (White, Black, Asian, Other)
- Country
- Ethnicity
- Weight (<64.0 kg, 64.0 – <74.0 kg, 74. 0 – < 83.0 kg, ≥ 83.0 kg)
- BWI (<25 kg/m^2, 25 kg/m^2 - <30 kg/m^2, ≥30 kg/m^2)
- Type of bleeds (spontaneous, traumatic)
- Previous treatment (on-demand, prophylaxis)
- Location of bleed (joint, muscle)

Sample size determination and interim analysis for sample size re-estimation

The trial had two co-primary endpoints for the Main Phase that both needed to succeed for the trial to succeed. The two endpoints were considered approximately independent and combined power then becomes the product of the individual power for each co-primary endpoint.

Power for the first co-primary endpoint: incidence rate of FVIII-inhibitors ≥ 0.6 BU

Given the rarity of the disease, a sample size of 105 subjects treated for a minimum of 50 exposure days was proposed to allow for a reasonable evaluation of inhibitor formation in this trial.

The aim was to demonstrate that the upper confidence limit for the inhibitor rate was below 6.8%. In practical terms this would happen if 2 or less inhibitors were observed in the planned 105 subjects with 50 exposure days. If the true inhibitor rate of N8-GP is 0.5% then the chance/power to achieve a maximum of 2 inhibitors out of 132 subjects who entered into the trial would be 97%.

Power for the second co-primary endpoint: ABR in the prophylaxis arm
The true bleeding rate was assumed to be 6.8 as for historical prophylaxis data (see statistical methodology for more information in this section) but for the sample size calculation it was assumed that 1 subject would withdraw within 1 month and that would lift the effective annualized bleeding rate for the power calculation by 24/120 = 0.2, i.e. from 6.8 to 7.0.

The ABR was estimated based on a Poisson regression model allowing for over-dispersion and using log observation time as offset to account for the differing treatment lengths. Based on an approximation to the normal distribution and assuming that the subjects bleed 7.0 times per year and an over-dispersion of 5 (variance 35), 120 subjects entered on prophylaxis would give a power of 79%.

The power calculation is sensitive to the assumed over-dispersion (OD) of 5. An interim analysis was performed to evaluate the OD when approximately 90 subjects had been recruited to prophylaxis: If the estimated OD for the full study was larger than 6, then the sample size would be adjusted up to 160 subjects on prophylaxis from originally 120 in order to ensure that the power holds.

Combined power
With 97% power for the first co-primary endpoint and 79% power for the second co-primary endpoint the combined power for the study with the given original sample size (120 prophylaxis and 12 on-demand) was expected to be about 97%*79% = 76%.

Approximately 172 subjects were planned to be enrolled in the Main Phase of the trial including at least 12 subjects (10 to complete the trial) in on-demand treatment and 160 subjects in prophylaxis treatment (145 to complete the trial) after the adjustment of the sample size as a result of the interim analysis.

Handling of missing data
All missing or partial data were to be presented as missing in the subject data listings as they were recorded on the CRF. The following imputation rules were to be implemented so as not to exclude subjects from statistical analyses due to missing or incomplete data:

- If a bleed has a missing date/time, then the date of the associated infusion will be used as the bleed date/time. If the infusion for a bleed has a missing date/time, then the associated bleed will be used to determine the infusion date/time.
- For subjects in both the prophylaxis and on-demand treatment arm, if there was no information regarding the AE start day, or there was partial information that AE started after treatment, the missing AE start day was to be imputed as first day of dosing in the clinic at Visit 2. If there was information that AE occurred before the treatment, the date of the day prior to the treatment day was to be used. Missing end date for an AE was not to be imputed.

In the primary efficacy analyses, the bleeding rates were to be imputed for subjects who withdrew prematurely. If e.g. a subject withdrew after 2 months with 3 bleeding episodes, but the subject should have been in the trial for 12 months, this subject counted as having had 18 bleeding episodes in 12 months. This was similar to LOCF and avoided positive bias occurring from subjects with many bleeding episodes withdrawing early. For subjects who withdrew within 1 month, imputation was conducted by assuming an annualized bleeding rate of 24 for the missing period.

Reviewer comment: *Although I think the applicant's imputation approach for the primary efficacy analysis is appropriate, I do not think it is similar to LOC and one should not use this term to report the analysis results.*

Statistical methodology
The study had two co-primary endpoints that both had to succeed.

Incidence rate of FVIII-inhibitors ≥0.6 BU
The rate of inhibitors was to be reported and 1-sided 97.5% upper confidence limit was to be provided based on an exact calculation for a binomial distribution. For the calculation of the inhibitor rate the nominator was to include all subjects with neutralizing antibodies while the denominator was to include all subjects with a minimum of 50 exposure days plus any subjects with less than 50 exposure days but with inhibitors. Adequate safety with regard to inhibitors was to be concluded if the upper 1-sided 97.5% confidence limit was below 6.8% corresponding to the upper 97.5% confidence limit if 2 inhibitors out of 105 subjects were observed (3 or less if the study should get 127 or more subjects with 50 exposure days).

ABR for subjects receiving prophylaxis treatment
The prophylactic effect of N8-GP was to be shown by comparison of the observed bleeding rates to historical data on annualized bleeding rates for subjects treated on-demand and prophylaxis.

In a systematic review of the treatment of hemophilia A studies comprising 20 subjects or more, 9 studies were selected to estimate an overall mean ABR by the following criteria: 1) The subjects had hemophilia A with an endogenous FVIII activity < 2%. 2) The authors had defined and described the prophylactic regimen. 3) The mean annualized bleeding rate was reported or could be calculated from the results in the publication. In the calculation, the bleeding rate from each trial was weighted by number of subjects in the trial. Based on this, Novo Nordisk suggested that representative numbers for mean ABR in severe hemophilia subjects are 24 bleeds/year for subjects treated on-demand and 6.8 bleeds/year for subjects on prophylactic treatment.

Prophylactic effect of N8-GP would be concluded, if the bleeding rate was significantly below 50% of the historical on-demand bleeding rate (i.e. significantly lower than 12) as well as within 25% of the historical prophylaxis bleeding rates (i.e. significantly lower than 6.8*1.25 = 8.5). Since both must be met in practice it must be shown that the bleeding rate is significantly lower than 8.5.

Let AR be the true yearly bleeding rate. The null-hypothesis was tested against the alternative hypothesis as given by:

H_0: AR ≥ 8.5 against H_A: AR < 8.5
The endpoint was to be analyzed by a Poisson regression model on number of bleeding episodes per subject allowing for over-dispersion (using Pearson's chi-square divided by the degrees of freedom [i.e. Scale=Pscale in SAS]) and using log planned observation duration as an offset. Estimates of the ABR were provided with 95% confidence intervals.

Since the expected exposure time for each subject in the Main Phase of the trial depends on when the subject was recruited in the trial, the maximum expected exposure time based on the last visit date included in each part of the analysis was to be used.

Confirmatory secondary endpoint: Hemostatic effect of N8-GP when used for treatment of bleeding episodes
This endpoint was to be assessed as success/failure based on a four-point scale for hemostatic response (excellent, good, moderate and none). Excellent and good was to be counted as success and moderate and none as failure. In addition, any bleeding episode with missing response information was to be counted as failures.

A success rate of 80% was considered the goal. Due to variation it was not certain that N8-GP would achieve an observed 80% success rate in this trial even if the true success rate was 80%. For that reason, it was to be demonstrated that the success rate for N8-GP is at most 15% (absolute) worse than 80%.

Let R be the true success rate. The null-hypothesis was to be tested against the alternative hypothesis as given by:
H_0: R ≤ 65% against H_A: R > 65%
This was to be assessed by a logistic regression. The analysis was to be performed by use of Proc Genmod in SAS. Correlation within subjects was to be taken into account using a generalized estimation equations approach with a working correlation matrix with a compound symmetry structure. Adequate efficacy would be concluded if the 1-sided lower 97.5% confidence limit for the success rate was above 65%.

Extension 1: ABR for subjects receiving q7D 75 IU/kg prophylaxis treatment
Estimates of the ABR for each randomized regimen were to be provided with 95% confidence intervals. Treatment effect of every 7 day dosing was to be concluded if the upper limit of the 95% CI is below 8.5. In addition, the two randomized treatment regimens were to be compared by reporting the estimated ratio between the two randomized treatment regimens with corresponding 95% confidence interval.

<u>Sensitivity analysis</u>
ABR for subjects receiving prophylaxis treatment

- Analysis applying a different model

A sensitivity analysis based on a negative binomial regression model with number of bleeding episodes requiring treatment as the outcome variable and adjusting for exposure time was to be performed.

- Analysis without imputation to planned trial duration

The primary prophylaxis analysis was to be repeated without imputing number of bleeding episodes for any withdrawals. In this analysis, only the observed bleeding episodes were to be counted and the offset would be the actual observation duration rather than the planned.

Confirmatory secondary endpoints

- Analysis on observed responses only (i.e. excluding missing observations):

A sensitivity analysis was to be performed similar to the primary analysis but only analyzing bleeding episodes with recorded responses (i.e. not counting any bleeding episodes with missing response as failures).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

FAS and SAS are identical in the Main Phase, Extension 1 and Extension 2 of the trial. A total of 186 subjects were included in these analysis sets. No subjects were excluded from any analyses.

6.1.10.1.1 Demographics

The trial population consisted of male subjects with severe hemophilia A. The median age was 29.0 years (ranging from 12 to 66 years) (Table 2).

The mean body weight of all subjects was 75.5 kg (ranging from 39 to 122 kg). The majority of the subjects were White (74.2%); the second largest group was Asian (18.8%). A total of 24.7% of the subjects were from the US, 11.8% were from the United Kingdom, 8.1% were from Japan and 7.0% were from Germany, while the remaining subjects were distributed between the other 18 countries. Mean age was lower in the prophylaxis arm (30.6 years) as compared to the on-demand arm (39.8 years) since all the 25 adolescent subjects enrolled in the trial were in the prophylaxis arm. In the Extension 1, mean age was slightly lower in the q4D arm (26.4 years) as compared to the q7D arm (30.9 years). Limited blacks and Hispanics subjects were included in the trial. However, since the predilection for clinical bleeding is dependent on the degree of factor VIII deficiency, race and ethnicity related differences in efficacy are expected to be minimal.

Table 2 Baseline Demographics and body measurements (FAS)

	Prophylaxis	On-demand	Total
Number of patients*	175	12	186
Age at baseline (years)			
N	175	12	186
Mean (SD)	30.6 (12.5)	39.8 (13.9)	31.1 (12.6)
Median	29.0	43.0	29.0
Min ; Max	12 ; 66	22 ; 60	12 ; 66
Ethnicity, N (%)			
N	175 (100.0)	12 (100.0)	186 (100.0)
Hispanic or Latino	13 (7.4)	-	13 (7.0)
Not Hispanic or Latino	162 (92.6)	12 (100.0)	173 (93.0)
Race, N (%)			
N	175 (100.0)	12 (100.0)	186 (100.0)
Asian	31 (17.7)	4 (33.3)	35 (18.8)
Black or African American	8 (4.6)	3 (25.0)	11 (5.9)
White	134 (76.6)	5 (41.7)	138 (74.2)
Other	2 (1.1)	-	2 (1.1)
Height (cm)			
N	175	12	186
Mean (SD)	175.3 (7.8)	174.0 (8.4)	175.3 (7.8)
Median	175.0	174.8	175.0
Min ; Max	153 ; 198	159 ; 187	153 ; 198
Body weight (kg)			
N	175	12	186
Mean (SD)	75.0 (14.4)	73.5 (12.8)	75.0 (14.3)
Median	74.0	72.6	74.0
Min ; Max	39 ; 122	55 ; 101	39 ; 122
BMI (kg/m^2)			
N	175	12	186
Mean (SD)	24.3 (3.9)	24.3 (4.4)	24.3 (3.9)
Median	23.9	22.6	23.9
Min ; Max	15 ; 35	19 ; 34	15 ; 35

* One patient changed treatment regimen from on-demand to prophylaxis at Visit 6. Therefore he is included in both the prophylaxis and on-demand arm but only counted once in the total.
The baseline value for height is the measurement at screening (Visit 1)
The baseline value for weight is the value from Visit 2a
If the Visit 2a value for weight is missing, the value from Visit 1 is used as baseline
BMI: body mass index

Source: Adapted from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase CSR, Tables 10-3 and 10-4

6.1.10.1.2 Disease Characterization of the Enrolled Population

All subjects were previously treated, with a history of at least 150 EDs to other FVIII products and no history of inhibitors. In all, 90 subjects had relatives with hemophilia A. None of the subjects enrolled had clinical suspicion of inhibitors.

Before entry to the trial, 149 subjects (80.1%) received regular prophylactic treatment; 13 subjects used plasma-derived FVIII products and 136 used recombinant products. The remaining 37 subjects (19.9%) followed an on-demand treatment regimen. In the subgroup of adolescent subjects, all but one of the subjects (95.8%) was receiving prophylactic treatment with either recombinant or plasma-derived FVIII products. A total of 68 subjects (43.9%) had intron 22 inversion genotype.

At baseline, 10 subjects were positive for HIV antibodies, 109 subjects were positive for hepatitis C antibodies and 6 subjects were positive for hepatitis B antibodies; all of these were adult subjects.

The mean number of bleeds in the previous 12 months was 9.9 (SD: 26.7) in 147 subjects.

6.1.10.1.3 Subject Disposition

A total of 215 subjects were screened and 186 subjects were dosed with N8-GP, of whom 25 subjects were adolescents (12−17 years). A total of 165 subjects completed the Main Phase of the trial, and 150 continued into the Extension 1, of whom 139 completed 6 months of treatment in part 1 and continued into part 2.

In the Extension 1, a total of 55 subjects were randomized, 38 subjects were included in the q7D arm and 17 in the q4D arm. Total of 9 (24%) of the 38 subjects who were randomized to the q7D regimen switched to q4D dosing during Ext 1 (8 due to bleeding events and 1 due to investigator's discretion). Two of these subjects who switched to q4D dosing regimen did so within the first month. One additional subject discontinued from Ext 1 due to AE of ankle fracture.

An overview of subject disposition is provided in Table 3 and the flow of subjects in the trial is provided in Figure 1.

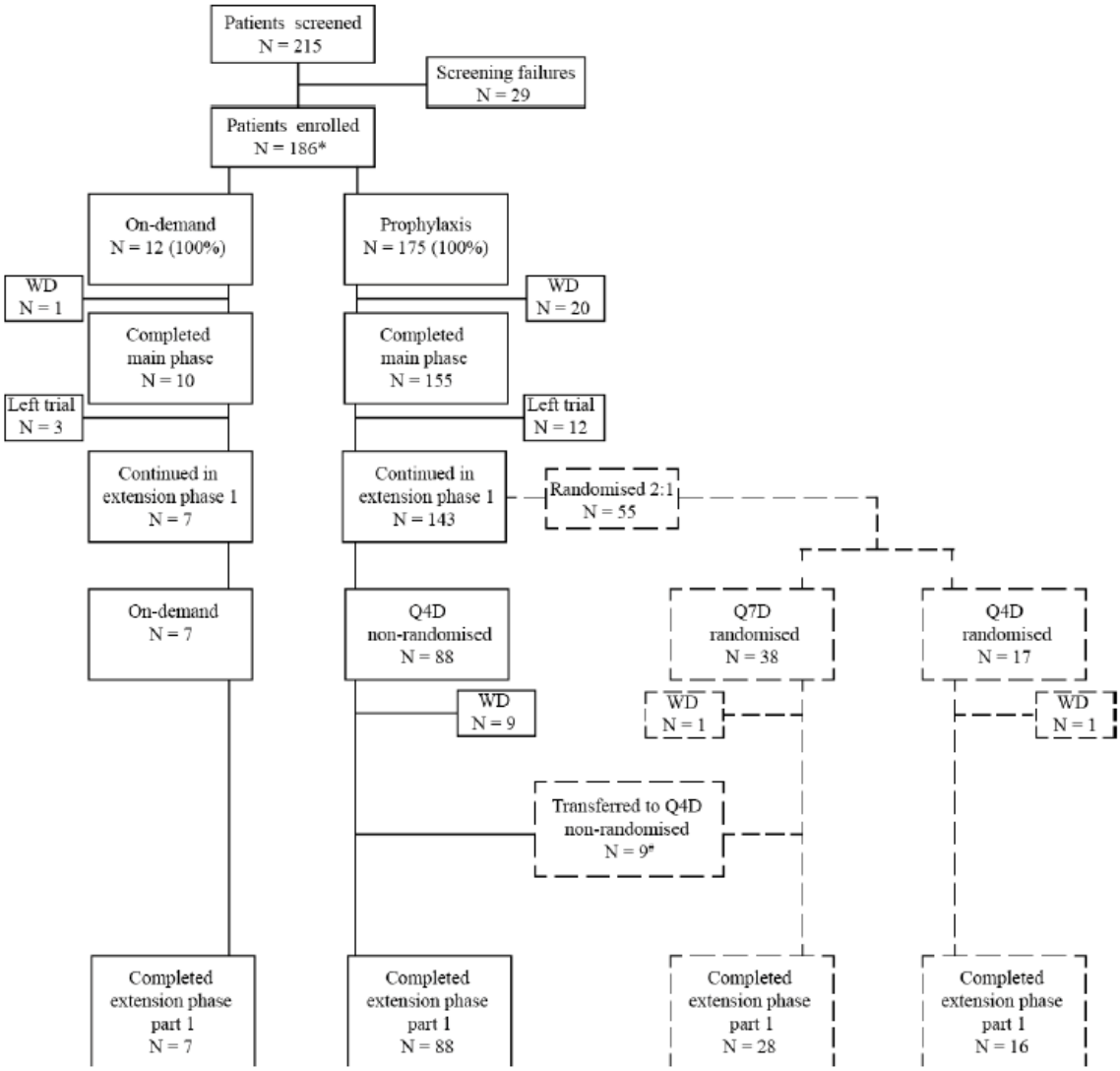
Table 3 Subject Disposition

	N8-GP 50 U/kg prophylaxis	N8-GP 75 U/kg prophylaxis	N8-GP 20-75 U/kg on-demand	Total
Screened				215
Exposed*	177 (100.0)	61 (100.0)	12 (100.0)	186 (100.0)
Withdrawal in main phase	20 (11.3)	NA	1 (8.3)	21 (11.3)
Ineff. therapy	1 (0.6)	NA	-	1 (0.5)
Non-compliance	3 (1.7)	NA	-	3 (1.6)
Other	4 (2.3)	NA	-	4 (2.2)
Withdrawal criteria	12 (6.8)	NA	1 (8.3)	13 (7.0)
Number of patients with <1 month of exposure	6 (3.4)	NA	-	6 (3.2)
Change of treatment regimen+	-	NA	1 (8.3)	1 (0.5)
Completed main phase	155 (87.6)	NA	11 (91.7)	165 (88.7)
Not continued into extension phase**	12 (6.8)	NA	3 (25.0)	15 (8.1)
Continued in extension phase++	143 (80.8)	NA	7 (58.3)	150 (80.6)
Started extension part 1***	105 (59.3)	38 (62.3)	7 (58.3)	150 (80.6)
Withdrawal in extension part 1	10 (5.6)	1 (1.6)	-	11 (5.9)
Ae	4 (2.3)	1 (1.6)	-	5 (2.7)
Other	1 (0.6)	-	-	1 (0.5)
Withdrawal criteria	5 (2.8)	-	-	5 (2.7)
Change of treatment regimen#	-	9 (14.8)	-	9 (4.8)
Completed extension part 1	104 (58.8)	28 (45.9)	7 (58.3)	139 (74.7)

* One patient changed treatment regimen from on-demand to prophylaxis during main phase, and is counted as exposed in both the prophylaxis and on-demand arm, but counted only once in the total.
**These patients have completed main phase but will not continue into the extension phase.
***on this regimen
9 patients left randomisation and continued on Q4D regimen.
##Excluding time in surgery trial, if any.
The symbol '-' indicates zero observations.
ED: exposure days, AE: adverse event

Source: Adapted from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase and Extension 1 CSR, Table 10-1.

Figure 1 Subject Flowchart



* One patient changed treatment regimen from on-demand to prophylaxis during main phase, and is counted as exposed in both the prophylaxis and on-demand arm, but counted only once in the total.

Eight (8) patients were transferred due to bleeding episodes, and 1 patient was transferred on investigator's discretion.

Source: Adapted from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase and Extension 1 CSR, Figure 10-1.

Reviewer comment: *65 (54%) of 120 subjects at start of Ext 1 who met the randomization eligibility criteria chose not to be randomized to q7D dosing and only 55 subjects agreed to be randomized. The Applicant did not provide justification for why many subjects chose not to be randomized. Upon further request, the Applicant stipulated that based on communication with some investigators, subjects refusal to the randomization could be due to the requirement for more frequent monitoring if subjects were to be randomized.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

Main Phase

A total of 968 bleeds were treated with N8-GP in 117 subjects with bleeds during the trial. Most of the bleeds (68.8%) were spontaneous, 30.3% were traumatic bleeds and 0.9% were after minor surgery. In the prophylaxis arm 60% of the subjects had at least one bleeding episode treated with N8-GP, while all 12 subjects in the on-demand arm reported at least one bleeding episode. The most frequent location of bleeds was in the joint, which accounted for 65.5% of the 968 bleeds. The bleeds were classified as mild/moderate in 99.2% of the cases, and 8 bleeds (0.8%) were classified as severe. The mean duration of bleeds for the 916 bleeds with reported information on duration was approximately 28.1 hours.

The main differences between adolescents and adults were higher frequency of traumatic bleeds among adolescents (55.2%) compared with adults (28.4%), and a longer mean duration of bleeds among the adolescents (45.5 hours) compared with adults (27.1 hours).

Reviewer comment: *In the efficacy analyses, non-treatment requiring bleeding episodes that coincided with regular prophylaxis doses were not included. FDA asked the applicant to justify the reason for exclusion of the non-treatment requiring bleeds in the efficacy analyses in an IR sent on December 11, 2018. In the response, the Applicant stated that the main objective of the trials was to evaluate the prophylactic effect of N8-GP for prevention of clinically relevant bleeds. Non-treatment requiring bleeds (e.g., bruises, minor nose/gum bleeds) were not considered relevant for the assessment of ABRs in the clinical trials. These non-treatments requiring bleeds are bleeds that resolved by themselves or by the RICE principle (rest, ice, compression, elevation). However, upon our review, we noted that of the 26 non-treatment required bleeds, 16 bleeds occurred in the joints in 14 subjects. Some subjects had severe, spontaneous, or multiple joint bleeds and were not counted in the bleeding analyses of ABRs based on the subjects' or investigators' assessments. Therefore, FDA requested the applicant to provide additional efficacy analyses by including the non-treatment required bleeds for further review. These analyses are included in section 6.1.11.5 of this memo and are reviewed as post-hoc analyses.*

<u>Co-primary endpoint – ABR for subjects receiving prophylaxis treatment</u>

Estimates of the ABR using the Poisson regression model are presented together with the 95% confidence intervals for all subjects in Table 4. The ABR in the prophylaxis arm was estimated to be 3.70 (95% CI: 2.94; 4.66) with the upper limit of 95% CI below 8.5. The mean ABR was 3.73 (SD: 5.90). The median ABR was 1.33 (IQR: 0.00; 4.61).

Reviewer comment: *Among the 12 subjects withdrawn in the prophylaxis arm, 7 of them had less than 30 days of exposure of N8-GP. The Applicant's primary analysis was based on imputed ABRs as discusses in section 6.1.9 of this memo. Sensitivity analysis was repeated based on observed data without any imputation. The estimated ABR was 3.04 (95% CI: 2.45; 3.77) when no imputation was performed for withdrawn subjects. The corresponding median ABR was 1.18 (IQR: 0.00; 4.25). Sensitivity analyses were also performed by applying a negative binomial regression*

model as discussed in section 6.1.9 of this memo, the results of all analyses based on this model were consistent with those obtained based on the Poisson model.

Table 4 Annualized bleeding rate, Main Phase (FAS)

	Prophylaxis	On-demand	Total
Number of patients*	175	12	186
Number of patients with bleeds, N (%)	105 (60.0)	12 (100.0)	117 (62.9)
Number of patients with LOCF	12	1	13
Number of observed bleeds	436	532	968
Number of bleeds using imputation**	576	539	1115
Number of patients with less than 1 month exposure	7	0	7
Bleeds per patient (min ; max)	0.0 ; 45.0	7.0 ; 131.0	0.0 ; 131.0
Mean treatment period (years)***	0.89	1.35	0.92
Individual ABRs			
N	175	12	186
Mean (SD)	3.73 (5.90)	31.95 (19.09)	5.48 (9.99)
Median	1.33	30.87	1.60
Interquartile range	0.00 ; 4.61	18.64 ; 38.51	0.00 ; 5.88
Min ; Max	0.00 ; 28.42	4.75 ; 74.18	0.00 ; 74.18
Poisson estimate of ABR+	3.70	-	-
95% CI	2.94 ; 4.66	-	-
P-value++	<0.001	-	-
Negative binomial estimate of ABR+++	3.70	-	-
95% CI	2.93 ; 4.66	-	-
P-value++	<0.001	-	-

The analysis is based on a Poisson regression model allowing for over-dispersion. For patients withdrawing prematurely, the log planned observation duration is used as offset; for completers, the log actual observation duration is used.
* 1 patient who switched from on-demand to prophylaxis during the trial is counted in both columns.
** Imputation: For patients withdrawing prematurely, the number of bleeding episodes is imputed up to what would be expected if they had completed the trial, as described in the protocol. For patients withdrawing within one month, the annual bleeding rate is imputed as 24 episodes per year for the missing period.
*** For patients withdrawing prematurely, the planned observation duration is used; for completers, the actual treatment period is used.
+ Primary results based on a Poisson model, as specified in the protocol.
++ P-values are from the 1-sided test of the null hypothesis that the ABR is at least 8.5 evaluated at the 2.5% level.
+++ Additional sensitivity analysis based on a negative binomial model.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase CSR, Table 11-2.

Extension 1

Of the subjects treated in the q4D regimen (randomized and non-randomized) 66.3% had at least one bleeding episode treated with N8-GP, in the q7D arm 42.1% of the subjects had at least one bleeding episode treated with N8-GP. The mean duration of bleeds was 62.2 hours in the q7D arm, 24.1 hours in the q4D arm and 27.2 hours in the on-demand arm.

<u>ABR for subjects receiving q7D 75 IU/kg prophylaxis treatment</u>

Estimates of the ABR using the Poisson regression model are presented together with the 95% confidence intervals for all subjects in Table 5. The ABR in the q7D prophylaxis arm was estimated to be 3.57 (95% CI: 2.13; 6.00). The mean ABR was 3.59 (SD: 6.62). The median ABR was 0.00 (IQR: 0.00; 2.36). Subjects randomized to q4D with 50 IU/kg had an ABR estimated to 1.77 (95% CI: 0.59; 5.32). The mean ABR was 1.77 (SD: 2.42). The median ABR was 0 (IQR: 0.00; 2.23).

Table 5 Annualized bleeding rate for randomized subjects -Main Phase and Extension 1 (FAS)

	N8-GP 50 U/kg prophylaxis Q4D	N8-GP 75 U/kg prophylaxis Q7D	Total
Number of patients	17	38	55
Number of patients with bleeds, N (%)	8 (47.1)	16 (42.1)	24 (43.6)
Number of patients with LOCF	1	8	9
Number of observed bleeds	13	25	38
Number of bleeds using imputation*	14	63	77
Number of patients with less than 1 month exposure	0	2	2
Bleeds per patient (min ; max)*	0 ; 4	0 ; 12	0 ; 12
Mean treatment period (years)**	0.465	0.464	0.464
Individual ABRs			
Mean (SD)	1.77 (2.42)	3.59 (6.62)	3.03 (5.70)
Median	0.00	0.00	0.00
Interquartile range	0.00 ; 2.23	0.00 ; 2.36	0.00 ; 2.36
Min ; max	0.00 ; 8.49	0.00 ; 26.09	0.00 ; 26.09
Poisson estimate of ABR+	1.77	3.57	3.02
95% CI	0.59 ; 5.32	2.13 ; 6.00	1.83 ; 4.96
P-value++	0.003	<0.001	<0.001
Poisson estimate of Ratio			2.02
95% CI			0.60 ; 6.80
Negative binomial estimate of ABR+++	1.77	3.59	3.03
95% CI	0.69 ; 4.56	2.01 ; 6.42	1.83 ; 5.01
P-value++	<0.001	0.002	<0.001
Negative binomial estimate of Ratio			2.03
95% CI			0.67 ; 6.15

The analysis is based on a Poisson regression model allowing for over-dispersion. For patients withdrawing prematurely, the log planned treatment duration is used as offset; for completers, the log actual treatment duration is used.
* Imputation: For patients withdrawing prematurely, the number of bleeding episodes is imputed according to the planned treatment duration. For patients with <1 month of exposure, the annual bleeding rate is imputed as 24 episodes per year for the missing period.
** For patients withdrawing prematurely, the planned treatment duration is used; for completers, the actual treatment duration is used.
+ Primary results based on a Poisson model, as specified in the protocol.
++ P-values are from the 1-sided test of the null hypothesis that the ABR is at least 8.5 evaluated at the 2.5% level.
+++ Additional sensitivity analysis based on a negative binomial model.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase and Extension 1 CSR, Table 11-1.

Reviewer comment: *The Applicant's primary prophylaxis analysis was based on imputed ABRs as discusses in section 6.1.9 of this memo. Sensitivity analysis was repeated based on observed data without any imputation. The ABR in the q7D prophylaxis arm was estimated to be 1.65 (95% CI: 0.87; 3.13) when no imputation was performed for withdrawn subjects. The mean ABR was 3.37 (SD: 6.19). The median ABR was 0.00 (IQR: 0.00; 2.36). Subjects randomized to q4D with 50 IU/kg had an ABR estimated to 1.66 (95% CI: 0.69; 4.04). The mean ABR was 1.68 (SD: 2.34). The median ABR was 0 (IQR: 0.00; 2.23).*

Reviewer comment: *During the Extension 1, 9 (24%) of the 38 subjects who were randomized to the q7D regimen switched to q4D dosing during Extension 1 (8 due to bleeding events and one subject due to investigator's recommendation). In addition, one subject discontinued the q7D regimen due to AE of ankle fracture. For the 10 subjects who didn't complete the q7D regimen, 2 of them had less than 1-month exposure of N8-GP. These 10 subjects were handled as withdrawals in the primary analyses by using the imputation method specified in section 6.1.9 of this memo. The ABR assessment shows that the ABR in subjects who received the q7D regimen was approximately double the ABR in subjects who received the q4D regimen (Poisson estiamtes:3.57 vs 1.77; Mean: 3.59 vs 1.77). Therefore, given the number of subjects who required rescue treatment and change to a more frequent dosing and the higher ABR in the q7D regimen, I do not recommend including this dosing regimen in the label due to the increased risk of bleeding under this regimen even for the selected subjects with a lower risk of bleeding (only subjects on prophylaxis with 0−2 bleeds during the last 6 months of the Main Phase had the option of being randomized in Extension 1). Inability to identify characteristics of subjects who are likely to benefit*

from an every 7-day regimen and in the absence of pre-specified eligibility criteria to define this group of subjects will expose the subjects in a substantial risk of bleeding episodes.

6.1.11.2 Analyses of Secondary Endpoints

Main Phase

Confirmatory secondary endpoint – hemostatic effect of N8-GP when used to treat bleeds

A summary of hemostatic responses and success rates for all subjects is presented in Table 6. Out of the 968 bleeding episodes in the trial, 964 bleeds were rated, while rating of 4 bleeds was missing. The estimated success rate using the logistic regression model for all bleeds (including missing responses as failure) was 84.2% (95% CI: 80.0; 87.7), and thereby above the 80% which was the pre-specified goal for the success rate. The observed the success rate for all bleeds (including missing responses as failure) was 88.4%.

The success rate for treatment of bleeds was higher in subjects receiving on-demand treatment than in subjects receiving prophylaxis treatment.

Table 6 Hemostatic response, Main Phase (FAS)

	N8-GP 50 U/kg prophylaxis	N8-GP 20-75 U/kg on-demand	Total
Number of patients	175	12	186
Number of patients with bleeds *	105	12	117
Number of bleeds *	436	532	968
Haemostatic response, N (%)			
N	436 (100.0)	532 (100.0)	968 (100.0)
Excellent	192 (44.0)	320 (60.2)	512 (52.9)
Good	174 (39.9)	170 (32.0)	344 (35.5)
Moderate	62 (14.2)	41 (7.7)	103 (10.6)
None	4 (0.9)	1 (0.2)	5 (0.5)
Missing	4 (0.9)		4 (0.4)
Success/Failure (including missing as failure), N (%)			
N	436 (100.0)	532 (100.0)	968 (100.0)
Success	366 (83.9)	490 (92.1)	856 (88.4)
Failure	70 (16.1)	42 (7.9)	112 (11.6)
Success/Failure, N (%)			
N	432 (100.0)	532 (100.0)	964 (100.0)
Success	366 (84.7)	490 (92.1)	856 (88.8)
Failure	66 (15.3)	42 (7.9)	108 (11.2)
Success Rate (including missing as failure)			
Rate (%)	83.7	88.4	84.2
95% CI	(79.0; 87.5)	(80.0; 93.5)	(80.0; 87.7)
p-value**	<.001	<.001	<.001
Success Rate			
Rate (%)	84.6	88.4	85.1
95% CI	(79.9; 88.3)	(80.0; 93.5)	(80.9; 88.4)
p-value**	<.001	<.001	<.001

Analysed using logistic regression accounting for repeated measures within subject assuming compound symmetry working correlation.
* Only bleeds treated with N8-GP are included
** p-value is from the 1-sided test of the null hypothesis that the success rate is at least 65% at the 2.5% level.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase CSR, Table 11-4.

The hemostatic response was also analyzed by other factors, see Table 7. The total success rate was slightly higher for spontaneous compared with traumatic bleeds. Furthermore, differences between locations of bleeds were observed, but numbers of bleeds in some groups were small. Mucosal, subcutaneous and gastrointestinal bleeds had a higher success rate than the overall success rate, and muscular bleeds a slightly lower success rate. As expected, there was an association between increase in number of injections to treat a bleed and lower success rates. The

proportion of successfully treated bleeds that were resolved with 1 injection of N8-GP was 94.6%.

Table 7 Hemostatic response – success rates by factors, Main Phase (FAS)

Factor N (total number of successfully treated bleeds by factor) (%) Percentage of treatment successes by factor	Prophylaxis 50 U/kg	On-demand 20-75 U/kg	Total
Cause of bleed			
Spontaneous	211 (84.1)	386 (93.0)	597 (89.6)
Traumatic	153 (83.6)	97 (88.2)	250 (85.3)
Previous treatment			
Prophylaxis	273 (85.8)	-	273 (85.8)
On-demand	93 (78.8)	490 (92.1)	583 (89.7)
Location of bleed			
Joint	272 (83.7)	292 (94.5)	564 (89.0)
Muscular	46 (80.7)	72 (81.8)	118 (81.4)
Mucosal	13 (92.9)	22 (100.0)	35 (97.2)
Subcutaneous	11 (84.6)	80 (100.0)	91 (97.8)
Gastrointestinal	4 (100.0)	1 (100.0)	5 (100.0)
Others	20 (87.0)	23 (71.9)	43 (78.2)
Time from start of bleed until the first administration of N8-GP			
< 2 hours	220 (84.6)	270 (94.7)	490 (89.7)
2−4 hours	64 (88.9)	50 (92.6)	114 (90.5)
> 4 hours	82 (79.6)	170 (88.1)	252 (85.1)
Number of injections to treat bleed			
1 injection	312 (92.3)	453 (96.2)	765 (94.6)
2 injections	46 (65.7)	29 (64.4)	75 (65.2)
3 injections	5 (41.7)	5 (71.4)	10 (52.6)

Missing response are counted as failure
Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase CSR, Table 11-5.

Supportive secondary endpoint - Consumption of N8-GP (number of injections and IU/kg) per bleed

Of the total 968 bleeds in the trial, 83.6% were resolved with 1 injection of N8-GP, 11.9% were resolved with 2 injections; Therefore, 95.5% of bleeds were treated with ≤ 2 injections. In the prophylaxis arm 77.5% of the bleeding episodes were resolved with 1 injection of N8-GP, whereas the proportion was 88.5% for the on-demand arm. Furthermore, the highest number of injections to treat a bleed was 9 injections in the prophylaxis arm and 13 injections in the on-demand arm.

The per protocol dose level to be used for treatment of a bleeding episode was 20-75 IU/kg. The mean dose used to treat a bleed was 64.6 IU/kg in the prophylaxis arm, 41.0 IU/kg in the on-demand arm, and 51.6 IU/kg for all bleeds.

Extension 1

Confirmatory secondary endpoint – hemostatic effect of N8-GP when used to treat bleeds

A summary of hemostatic responses and success rates for all subjects is presented in Table 8. Out of the 1436 bleeding episodes in the trial, 1420 bleeds were rated, while rating of 16 bleeds was missing. The estimated success rate using the logistic regression model for all bleeds (including missing responses as failure) was 83.3%

(95% CI: 79.4; 86.6). The observed the success rate for all bleeds (including missing responses as failure) was 87.7%.

The success rate for treatment of bleeds was higher in subjects receiving on-demand treatment than in subjects receiving prophylaxis treatment.

Table 8 Hemostatic response, Main Phase and Extension 1 (FAS)

	N8-GP 50 U/kg prophylaxis Q4D	N8-GP 75 U/kg prophylaxis Q7D	N8-GP 20-75 U/kg on-demand	Total
Number of patients	175	38	12	186
Number of patients with bleeds*, N(%)	116 (66.3)	16 (42.1)	12 (100.0)	132 (71.0)
Number of bleeds*	716	25	695	1436
Haemostatic response, N(%)				
N	716 (100.0)	25 (100.0)	695 (100.0)	1436 (100.0)
Excellent	330 (46.1)	9 (36.0)	406 (58.4)	745 (51.9)
Good	270 (37.7)	11 (44.0)	233 (33.5)	514 (35.8)
Moderate	98 (13.7)	3 (12.0)	55 (7.9)	156 (10.9)
None	4 (0.6)	0 (0.0)	1 (0.1)	5 (0.3)
Missing	14 (2.0)	2 (8.0)	0 (0.0)	16 (1.1)
Success/failure (incl. missing as failure), N(%)				
N	716 (100.0)	25 (100.0)	695 (100.0)	1436 (100.0)
Success	600 (83.8)	20 (80.0)	639 (91.9)	1259 (87.7)
Failure	116 (16.2)	5 (20.0)	56 (8.1)	177 (12.3)
Success/failure, N(%)				
N	702 (100.0)	23 (100.0)	695 (100.0)	1420 (100.0)
Success	600 (85.5)	20 (87.0)	639 (91.9)	1259 (88.7)
Failure	102 (14.5)	3 (13.0)	56 (8.1)	161 (11.3)
Success rate (incl. missing as failure)				
Rate (%)	82.7	80.8	88.1	83.3
95% CI	78.1 ; 86.4	60.3 ; 92.1	80.1 ; 93.2	79.4 ; 86.6
p-value**	<.001	0.058	<.001	<.001
Success rate				
Rate (%)	84.6	87.1	88.1	85.1
95% CI	80.5 ; 87.9	67.9 ; 95.6	80.1 ; 93.2	81.5 ; 88.0
p-value**	<.001	0.015	<.001	<.001

Analysed using logistic regression accounting for repeated measures within subject assuming compound symmetry working correlation.
* Only bleeds treated with N8-GP are included
** p-value is from the 1-sided test of the null hypothesis that the success rate is at least 65% at the 2.5% level.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase and Extension 1 CSR, Table 11-3.

A summary of hemostatic responses and success rates for randomized subjects in Extension 1 is presented in Table 9. In the q7D prophylaxis arm, out of the 25 bleeding episodes in the trial, 23 bleeds were rated, while rating of 2 bleeds was missing. The estimated success rate using the logistic regression model for all bleeds in the q7D arm (including missing responses as failure) was 80.8% (95% CI: 60.3; 92.1). The observed the success rate (including missing responses as failure) was 80.0%. All 13 bleeding episodes occurred in the q4D arm were rated with 100% success rate.

Table 9 Hemostatic response for randomized subjects, Extension 1 (FAS)

	N8-GP 50 U/kg prophylaxis Q4D	N8-GP 75 U/kg prophylaxis Q7D	Total
Number of patients	17	38	55
Number of patients with bleeds*, N(%)	8 (47.1)	16 (42.1)	24 (43.6)
Number of bleeds*	13	25	38
Haemostatic response, N(%)			
N	13 (100.0)	25 (100.0)	38 (100.0)
Excellent	8 (61.5)	9 (36.0)	17 (44.7)
Good	5 (38.5)	11 (44.0)	16 (42.1)
Moderate	0 (0.0)	3 (12.0)	3 (7.9)
None	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	2 (8.0)	2 (5.3)
Success/failure (incl. missing as failure), N(%)			
N	13 (100.0)	25 (100.0)	38 (100.0)
Success	13 (100.0)	20 (80.0)	33 (86.8)
Failure	0 (0.0)	5 (20.0)	5 (13.2)
Success/failure, N(%)			
N	13 (100.0)	23 (100.0)	36 (100.0)
Success	13 (100.0)	20 (87.0)	33 (91.7)
Failure	0 (0.0)	3 (13.0)	3 (8.3)
Success rate (incl. missing as failure)			
Rate (%)	-	80.8	87.5
95% CI	-	60.3 ; 92.1	71.7 ; 95.1
p-value**	-	0.058	0.005
Success rate			
Rate (%)	-	87.1	91.8
95% CI	-	67.9 ; 95.6	77.7 ; 97.3
p-value**	-	0.015	0.001

Analysed using logistic regression accounting for repeated measures within subject assuming compound symmetry working correlation.
* Only bleeds treated with N8-GP are included
** p-value is from the 1-sided test of the null hypothesis that the success rate is at least 65% at the 2.5% level.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase and Extension 1 CSR, Table 14.2.249.

Supportive secondary endpoint - Consumption of N8-GP (number of injections and IU/kg) per bleed

Of the total 1436 bleeds in the trial, 82.2% were resolved with 1 injection of N8-GP, 12.8% were resolved with 2 injections; Therefore, 95.0% of bleeds were treated with ≤ 2 injections. In the prophylaxis arm 76.5% of the bleeding episodes were resolved with 1 injection of N8-GP in the q4D arm compared to 72% in the q7D arm, whereas the proportion was 88.3% for the on-demand arm. Furthermore, the highest number of injections to treat a bleed was 24 injections in the prophylaxis arm (q4D) and 13 injections in the on-demand arm.

The per protocol dose level to be used for treatment of a bleeding episode was 20-75 IU/kg. The mean dose used to treat a bleed was 67.8 IU/kg in the prophylaxis q4D arm and 78.2 IU/kg in the q7D arm, as compared to 39.3 IU/kg in the on-demand arm, reflecting that more bleeds in the on-demand arm were resolved with 1 injection and the on-demand subjects used a lower dose per injection.

6.1.11.3 Subpopulation Analyses

There were notable differences in the ABRs between countries with ABRs ranging from no bleed to 11.60, but the small number of subjects in some countries is notable. Furthermore, the ABR was investigated by race, ethnicity, weight and by body mass index. No apparent differences in the ABRs were observed for these subgroups.

6.1.11.4 Dropouts and/or Discontinuations

A total of 32 subjects were withdrawn during the trial, 21 in Main Phase and 11 in Extension 1. Five of the subjects withdrew due to AEs in the Extension 1.

A total of 21 subjects were withdrawn during the Main Phase of the trial (see Table 10); Of these, 6 subjects withdrew within the first month of exposure. Most reason for subjects discontinuation from the study were due to meeting the pre-specified withdrawal criteria (i.e., needs for surgery in countries where the surgery trial was not initiated yet, using other factor VIII products, personal logistical issues, or non-compliance).

A total of 38 subjects were randomized to q7D, and during the Extension Phase 9 of these subjects were transferred to q4D non-randomized. Eight subjects were transferred due to bleeding episodes, and 1 subject was transferred on the investigator's discretion.

Table 10 Subjects withdrawal, Main Phase and Extension 1

Characteristics		**Subjects N=186 (%)**
Withdrawal (Main Phase)	# of subjects	21 (11.3%)
Reason for Discontinuation	Lack of efficacy	1 (0.5%)
	Other	4 (2.2%)
	Non-compliance	3 (1.6%)
	Withdrawal criteria	13 (7.0%)
	Adverse events	0 (0%)
Withdrawal (Extension 1)	# of subjects	11(7.3%)
Reason for Discontinuation	Other	1 (0.7%)
	Withdrawal criteria	5 (3.3%)
	Adverse events	5 (3.3%)

Source: Adapted from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Main Phase and Extension 1CSR, Table 10-1.

6.1.11.5 Exploratory and Post Hoc Analyses

Analyses by including the non-treatment required bleeds

In addition to the 968 bleeds, 26 bleeds in 23 subjects that didn't require treatment were identified. A total of 650 joint bleeds occurred in the Main Phase of the trial. Of these, 16 were non-treatment requiring joint bleeds (13 in subjects on prophylaxis and 3 in subjects treated on-demand). No non-treatment requiring joint bleeds occurred during the randomized part of the Extension 1. Hence, the total number of bleeds becomes 994 in 119 subjects. Table 11 summarizes the ABRs by age, treatment regimen, and bleed type for treated bleeds and for all bleeds including the non-treatment required bleeds.

Table 11: Efficacy in adult/adolescent prophylaxis, median and mean ABRs by age, treatment regimen, and bleed type, Main Phase (FAS)

	Prophylaxis			On-demand
Age Range	**12–17 years**	**18–70 years**	**12–70 years**	**18–70 years**
# of subjects	25	150	175	12
Mean treatment duration (years)	0.85	0.81	0.82	1.33
Treated bleeds				
# of subjects (%)	19 (76)	86 (57)	105 (60)	12 (100)
# of bleeds	67	369	436	532
Median ABR (IQR)	2.22 (0.87;4.73)	1.17 (0.00;3.71)	1.18 (0.00;4.25)	30.87 (18.64;38.51)
Mean ABR (SD)	3.47 (3.85)	2.92 (4.78)	3.00 (4.66)	31.90 (19.08)
All bleeds				
# of subjects (%)	19 (76)	88 (59)	107 (61)	12 (100)
# of bleeds*	72	386	458	536
Median ABR (IQR)	2.22 (0.87;6.02)	1.18 (0.00;4.33)	1.20 (0.00;4.73)	31.25 (18.64;38.90)
Mean ABR (SD)	3.73 (4.06)	3.18 (5.06)	3.26 (4.92)	32.15 (19.12)
Treated spontaneous bleeds				
# of subjects (%)	11 (44)	65 (43)	76 (43)	12 (100)
# of bleeds	30	221	251	415
Median ABR (IQR)	0.00 (0.00;1.47)	0.00 (0.00;1.85)	0.00 (0.00;1.82)	19.35 (12.07;31.04)
Mean ABR (SD)	1.392.39)	1.80 (3.65)	1.74 (3.50)	24.46 (17.32)
Treated traumatic bleeds				
# of subjects (%)	16 (64)	57 (38)	73 (42)	10 (83)
# of bleeds	37	146	183	110
Median ABR (IQR)	1.33 (0.00;2.58)	0.00 (0.00;1.42)	0.00 (0.00;1.74)	4.32 (0.77;9.93)
Mean ABR (SD)	2.08 (2.88)	1.10 (2.21)	1.24 (2.33)	6.13(6.15)
Treated joint bleeds				
# of subjects (%)	16 (64)	74 (49)	90 (51)	12 (100)
# of bleeds	37	288	325	309
Median ABR (IQR)	1.22 (0.00;2.84)	0.00(0.00;2.84)	0.85 (0.00;2.84)	19.35 (4.48;28.76)
Mean ABR (SD)	1.76 (2.19)	2.32 (4.32)	2.24 (4.09)	19.67 (15.07)

*Post-hoc analysis was performed to include non-treatment required bleeds
Mean and Median ABRs are based on observed bleeding episodes without any imputation.
Source: Adapted from BLA 125671/0; Module 2.7.3 Summary of clinical efficacy, multiple tables; BLA amendment 125671/53, Module 1.11.3, multiple tables.

Reviewer comment: *The mean ABRs are increased when the analysis includes non-treatment requiring bleeds in both the prophylaxis and on-demand groups. However, this increase is minimal. Overall, all ABRs in the prophylaxis arm (with or without imputation and with or without including non-treatment requiring bleeds) are consistent with other FVIII products, therefore confirm the treatment effect of the 50 IU/kg every 4 day dosing regimen of the N8-GP for adult and adolescent subjects.*

6.1.12 Safety Analyses

The safety results were evaluated based on all the available data at the submission (Main Phase and two Extensions).

6.1.12.2 Incidence of inhibitors

Co-primary endpoint – Incidence rate of FVIII inhibitors

One adolescent subject developed FVIII inhibitors after 93 EDs to N8-GP during the Main Phase. This resulted in an estimated inhibitor rate of 0.6% and a one-sided 97.5% upper confidence limit for the inhibitor rate of 3.7% (Table 12). As this is

below the pre-specified limit of 6.8%, the result demonstrated adequate safety with regard to inhibitors.

Table 12 Incidence rate of inhibitory antibodies against FVIII (SAS)

	N8-GP prophylaxis	N8-GP on-demand	Total
Number of patients	177	12	186
Number of patients with inhibitor antibodies *	1	0	1
Number of patients at risk **	164	10	172
Rate of inhibitory antibodies***			
Estimated inhibitor rate	0.006	0.000	0.006
1-sided 97.5 % upper confidence limit	0.038	0.355	0.037

N8-GP prophylaxis includes patients with Q4D and Q7D exposure regimes
* All patients with neutralising antibodies are included in the numerator of the inhibitor rate (on-demand or prophylaxis).
** Any patient with a minimum 50 exposure days plus any patient with inhibitory inhibitors is included (irrespective of exposure numbers) in the denominator of the inhibitor rate.
3 patients changed treatment from on-demand to prophylaxis during the trial and are included at risk in both arms, except for patient (b) (6) This patient only had 20 on-demand exposure days and is therefore not included at risk in the on-demand arm.
*** Estimates of confidence limits are based on exact calculations for a binomial distribution.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3859 Results of the Main Phase, Extension 1 and interim results of Extension 2 of the trial, Table 14.2.13.

6.1.12.3 Deaths

One death occurred in a 67 year old subject with metastatic pancreatic carcinoma which was considered unlikely related to N8-GP by the investigator and Novo Nordisk.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 49 SAEs were recorded in 31 (16.7%) subjects. Two of these events (intervertebral discitis and factor VIII inhibition) were evaluated as possibly and probably, related to trial product by the investigator, respectively. These two events met the criteria for reporting as suspected unexpected serious adverse reaction (SUSAR). One subject had a non-treatment-emergent SAE. No thromboembolic events occurred during the trial.

6.2 NN7088-3860

NN7088-3859 study was titled “Efficacy and Safety of NNC 0129-0000-1003 (turoctocog alfa pegol) during Surgical Procedures in Patients with Hemophilia A”. This trial provides information on the bleeding-preventive effect during surgery, the hemostatic effect during and after these surgical procedures and the safety profile of N8-GP in subjects with hemophilia A.

6.2.1 Objectives (Primary, Secondary, etc.)

Primary objective:

- To evaluate the hemostatic effect of N8-GP during surgical procedures in subjects with hemophilia A

Secondary objectives:

- To evaluate the general safety of including immunogenicity of N8-GP when used for prevention and treatment of bleeding throughout the surgical period
- To evaluate the hemostatic effect of N8-GP during the post-operative period
- To evaluate the health economic (HE) resource use (hospitalization days) due to surgery

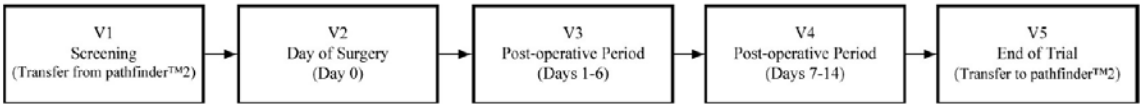
6.2.2 Design Overview

The trial was a multi-center, multi-national, open-label, non-randomized, single arm, efficacy and safety trial evaluating N8-GP during surgical procedures in subjects with severe (FVIII:C<1%) hemophilia A.

Subjects enrolled in this trial were recruited from trial NN7088-3859 and only if they had received ≥ 5 doses of N8-GP. Upon completion of this trial, subjects returned to trial NN7088-3859, reentering the prophylactic or on-demand treatment arm as per their prior participation in the trial. To ensure that at least 15 major surgical procedures could be evaluated in 10 to 15 subjects, it was estimated that 22 subjects needed to be screened.

The trial consisted of visits 1−5 for each individual subject. The trial period was estimated to have a total duration of 2−5 weeks (Figure 2).

Figure 2 Trial design



pathfinder™2 = NN7088-3859

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3860 CSR, Figure 9-1.

During days 1−6 in the post-operative period, assessments were done every day at the site. During days 7−14 in the post-operative period, assessments were done once at the site. Recruitment into this trial was not initiated until at least 20 bleeding episodes in at least 10 subjects had been treated with N8-GP in trial NN7088-3859.

6.2.3 Population

Key subject eligibility criteria:

- Ongoing participation in the (NN7088-3859) trial and having received ≥ 5 doses of N8-GP
- Undergoing major surgery requiring daily monitoring of FVIII:C and wound status for ≥ 3 days

6.2.4 Study Treatments

Subjects undergoing major surgery received bleeding preventive treatment with N8-GP before, during and after surgery. The dose level of N8-GP during this trial was chosen in accordance with the FVIII activity levels recommended by WFH Guidelines. The WFH guidelines for desired FVIII levels in major surgery are as follows: pre-surgery (day 0): 80−100%; post-surgery days 1−3: 60−80%; days 4−6: 40−60%; days 7−14: 30−50%. The maximum dose to be administered to a subject within 24 hours was 200 IU/kg.

Minor surgery performed post-operatively during the trial was not counted as surgery. Minor surgery could be performed while participating in this trial by administering an additional dose of N8-GP at 50−75 IU/kg or a dose sufficient to increase the FVIII level to 100% prior to the minor surgery to prevent peri-operative bleeding.

6.2.6 Sites and Centers

The trial was conducted at 25 sites in 13 countries as follows: Australia (1 site), Denmark (1 site), France (2 sites), Hungary (1 site), Israel (1 site), Italy (2 sites), Japan (3 sites), Malaysia (1 site), Netherlands (1 site), Switzerland (1 site), Turkey (3 sites), UK (4 sites) and US (4 sites).

6.2.8 Endpoints and Criteria for Study Success

Primary endpoint:

- Hemostatic effect during surgery evaluated by the four-point scale, assessed by the investigator/surgeon at the day of surgery
  Four-point response scale: excellent, good, moderate or none
  The following definitions were given:
  Excellent: Better than expected/predicted in this type of procedure
  Good: As expected in this type of procedure
  Moderate: Less than optimal for the type of procedure but haemostatic response maintained without change of treatment regimen
  None: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required.

Secondary efficacy endpoints:

- Estimated blood loss during surgery
- Average consumption of N8-GP during surgery
- Hemostatic effect of N8-GP during the post-operative period days 1−6
- Average consumption of N8-GP during the post-operative period days 1−6
- Number of transfusions during the post-operative period days 1−6
- Hemostatic effect of N8-GP during the post-operative period days 7−14

Safety endpoints:

- AEs and SAEs reported during the trial
- Incidence rate of inhibitors against FVIII (≥0.6 BU)

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations

- **FAS** – all subjects exposed to N8-GP. The FAS was used for analyses of primary and secondary efficacy endpoints.
- **SAS** – all subjects exposed to N8-GP. The SAS was used for analyses of safety endpoints.

The FAS and SAS were identical in this trial.

Sample size determination

Sample size was based on recommendations in the EMA guideline on the clinical investigation of recombinant and human plasma-derived FVIII products.

Statistical methodology

The hemostatic effect of N8-GP during surgery, evaluated according to a four-point scale (none, moderate, good, excellent) was summarized and listed based on descriptive statistics. The secondary efficacy and safety endpoints were also summarized and listed based on descriptive statistics.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The FAS and the SAS included all 34 dosed subjects, who all but one underwent a total of 45 surgeries.

6.2.10.1.1 Demographics

The demographics and body measurements at baseline are presented in Table 13. The trial population consisted of males with hemophilia A and with a mean age of 40.8 years (range: 15−69 years). One subject was adolescent (15 years of age), while the remaining subjects were adults. The majority of the subjects were White (82.4%) while 5 subjects (14.7%) were Asian and 1 subject (2.9%) were Black or African American.

Table 13 Baseline Demographics and body measurements (FAS)

	Total
Number of patients	34
Ethnicity, N (%)	
N	34 (100.0)
Not Hispanic or Latino	34 (100.0)
Race, N (%)	
N	34 (100.0)
Asian	5 (14.7)
Black or African American	1 (2.9)
White	28 (82.4)
Number of surgeries	45
Age at baseline (years)	
N*	48
Mean (SD)	40.8 (13.6)
Median	41.0
Min ; Max	15 ; 69
BMI (kg/m^2)	
N[b]	48
Mean (SD)	25.4 (4.4)
Median	25.0
Min ; Max	18.4 ; 36.7

Demographics are recorded at the NN7088-3859 screening visit and transferred to NN7088-3860.
Baseline age is recorded at the NN7088-3860 screening visit.
N: number of patients, N*: number of planned surgeries, SD: standard deviation,
%: percentage of patients.
Baseline BMI (height, body weight) is recorded at the NN7088-3860 screening visit.
BMI: body mass index, N[b]: number of surgeries, SD: standard deviation.
Three patients withdrew, having their surgical procedure cancelled or postponed,
two of whom, re-entered the trial and completed surgery.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3860 CSR, Table 10-2.

6.2.10.1.2 Disease Characterization of the Enrolled Population

A total of 17 of the 34 subjects had relatives with hemophilia A. Of those 17 subjects, 12 subjects had relatives with inhibitors. None of the subjects enrolled had clinical suspicion of inhibitors. At baseline (from trial NN7088-3859), 26 out of 34 subjects received prophylactic treatment with either recombinant or plasma-derived FVIII products. The remaining 8 subjects followed an on-demand treatment regimen.

6.2.10.1.3 Subject Disposition

A total of 34 subjects were screened in this trial. All 34 subjects were exposed to trial product and of these, 33 subjects completed the trial (Table 14). Three subjects were withdrawn during the trial due to withdrawal criterion no. 7 ('the planned major surgical procedure is cancelled or postponed'). Of these, 2 subjects re-entered the trial and completed surgery. A total of 45 surgeries were completed; 10 of the 33 subjects re-entered the trial: 4 subjects had 2 surgeries, 3 subjects had 3 surgeries, 1 subject had 4 surgeries and 2 subjects who initially withdrew re-entered the trial to have a surgery at a later time point.

Table 14 Subject Disposition

	Total
Number of screened patients	34
Number of exposed patients	34
Number of patients undergoing surgeries	33
Number of planned surgeries	48
Number of surgeries	45
Surgeries, N(%)	
Full analysis set	48 (100.0)
Safety analysis set	48 (100.0)
Completed	45 (93.8)
All surgery withdrawals, N(%)	3 (6.3)
Withdrawal criteria	3 (6.3)
Patients, N(%)	
Full analysis set	34 (100.0)
Safety analysis set	34 (100.0)
Completed	33 (97.1)
Years in trial	6.40
EDs in trial	979

ED: exposure days. %: percentage of patients.
Patients may undergo more than one surgery.
Three patients withdrew, having their surgical procedure cancelled or postponed, two of whom, re-entered the trial and completed surgery.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3860 CSR, Table 10-1.

6.2.11 Efficacy Analyses

A total of 45 surgeries were performed on 33 subjects. The procedures included 15 joint replacements, 9 arthroscopic orthopedic interventions, 17 other orthopedic interventions, and 4 non-orthopedic surgeries.

6.2.11.1 Analyses of Primary Endpoints

The hemostatic effect of N8-GP was rated as 'excellent' in 22 (48.9%) and as 'good' in 21 (46.7%) of the surgeries (Table 15), giving a success rate of 95.6%. Two surgeries (4.4%) had the effect rated as 'moderate'. No surgeries had an outcome rated as 'none'.

Table 15 Hemostatic effect of N8-GP during surgery (FAS)

	Total
Number of patients	34
Number of patients undergoing surgery	33
Number of surgeries	45
Haemostatic response	
N (%)	45 (100.0)
Excellent	22 (48.9)
Good	21 (46.7)
Moderate	2 (4.4)
None	0 (0.0)

N: number of surgeries, %: percentage of surgeries.
Patients may undergo more than one surgery.
During surgery is the time from knife to skin until last stitch
Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3860 CSR, Table 11-3.

6.2.11.2 Analyses of Secondary Endpoints

Estimated blood loss during surgery

The mean and median estimated blood loss following surgery was 339 mL and 50 mL, respectively. One subject had a markedly higher estimated blood loss (4520 mL) than the other subjects.

Average consumption of N8-GP during surgery

In all surgeries, subjects received a pre-surgery dose of N8-GP; the mean and median doses were 55.3 IU/kg and 51.2 IU/kg, respectively (range: 27.2−86.2 IU/kg). In 29 surgeries, subjects had a post-surgery dose administered; the mean and median doses were 31 IU/kg and 26.2 IU/kg, respectively (range: 10.1−58.8 IU/kg). All doses were administered as a single injection.

On the day of surgery, subjects received 1−3 doses of N8-GP: In 16 surgeries subjects received 1 dose, in 27 surgeries subjects received 2 doses and in 2 surgeries subjects received 3 doses.

6.2.12 Safety Analyses

6.2.12.3 Deaths

There were no deaths in the trial.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 5 serious adverse events were reported in 4 surgeries. Two of the serious adverse events were judged by the investigator as possibly related to trial product. Three serious adverse events reported in this trial were judged unlikely related to trial product by the investigator, and the outcome for these serious adverse events was reported as recovered or recovering.

6.3 NN7088-3885

NN7088-3885 study was titled “A multinational, open-label, non-controlled trial on safety, efficacy and pharmacokinetics of NNC 0129-0000-1003a in previously treated pediatric patients with severe hemophilia A”. The trial consisted of a Main Phase and an Extension Phase. The Extension Phase is still on-going at the time of the submission.

6.3.1 Objectives (Primary, Secondary, etc.)

Primary objective:

- To evaluate the immunogenicity of N8-GP

Key secondary objectives:

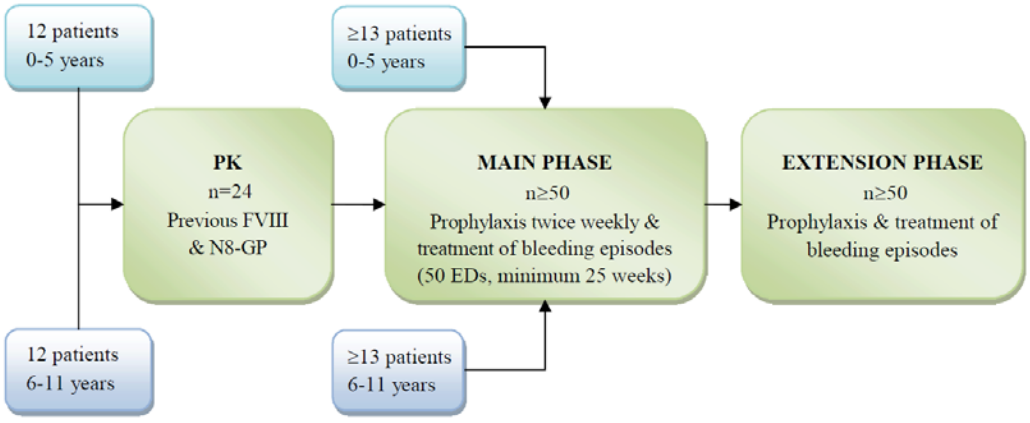
- To evaluate the safety other than immunogenicity of N8-GP
- To evaluate efficacy of N8-GP in prophylaxis and treatment of bleeding episodes

6.3.2 Design Overview

Trial NN7088-3885 was a multi-national, open-label, single-arm, and non-controlled trial to assess safety including immunogenicity, efficacy and PK of N8-GP. The trial product was given for prophylaxis and treatment of bleeding episodes to subjects below 12 years of age with severe hemophilia A. According to the EMA guideline >50 EDs in the 0–5 age group and >150 EDs in the 6–11 age group with previous FVIII products was required before any subjects were allowed to enter the trial.

The trial consisted of a Main Phase and an Extension Phase (see Figure 3). The duration of the Main Phase for each subject was approximately 26 weeks (corresponding to 50 EDs, which was a minimum requirement by the EMA guideline for evaluation of new FVIII products). The screening period added 2–6 weeks to each subject's trial participation. After completion of the Main Phase, the subjects could continue in an Extension Phase lasting until N8-GP is commercially available in the relevant countries or until the N8-GP programmed is terminated, or otherwise required by national regulations.

Figure 3 Trial overview



FVIII = factor VIII; N8-GP = glycopegylated recombinant coagulation factor VIII; PK = pharmacokinetics

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3885 Ext 1, CSR, Figure 9-1.

6.3.3 Population

Key subject eligibility criteria:

- Male subjects with severe congenital hemophilia A (FVIII activity level < 1%, according to medical records)
- Age below 12 years at screening (for Turkey only: Age above 3 and below 12 years at screening)

- Weight ≥10 kg at screening
- Documented history of > 150 EDs to FVIII products for subjects aged 6-11 years and > 50 EDs to FVIII products for subjects aged 0-5 years (for Turkey only: Documented history of > 50 EDs to FVIII products for subjects aged 6-11 years and > 50 EDs to FVIII products for subjects aged 3-5 years)

6.3.4 Study Treatments

The treatment regimen was prophylaxis twice weekly with approximately 60 IU/kg. All bleeds were to be treated with doses between 20–75 IU/kg.

6.3.6 Sites and Centers

The trial was conducted at 36 sites in 15 countries as follows: Canada (1 site), France (2 sites), Germany (1 site), Greece (2 sites), Israel (1 site), Italy (1 site), Japan (2 sites), Lithuania (1 site), Malaysia (1 site), Portugal (1 site), Switzerland (3 sites), Turkey (3 sites), Ukraine (2 sites), UK (3 sites), US (12 sites).

6.3.8 Endpoints and Criteria for Study Success

Primary endpoints:

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU

Secondary efficacy endpoints:

- Hemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for hemostatic response (excellent, good, moderate and non) by counting excellent and good as success and moderate and none as failure.
  The following definitions for response to treatment were suggested:
  Excellent: abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion;
  Good: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than one infusion for complete resolution;
  Moderate: probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than one infusion;
  None: no improvement, or worsening of symptoms.
- Number of bleeding episodes during prophylactic treatment with N8-GP (ABR)
- Consumption of N8-GP per bleeding episode (number of injections and IU/kg)
- Consumption of N8-GP during prophylaxis (number of injections and IU/kg per month and year)

6.3.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations

- **FAS** – All trial subjects allocated to treatment, for which at least one of the PK or efficacy endpoints was assessed, were included in the full analysis set. The FAS trial subjects were analyzed according to their received treatment.
- **SAS** – All subjects exposed to at least one dose of trial product were included in the safety analysis set. The trial subjects were analyzed according to the received treatment.

Sample size determination
No formal sample size calculations were performed. The sample size was based on the EMA guideline from July 2011 requirement.

Handling of missing data
The same as in section 6.1.9 of this memo.

Statistical methodology
Incidence of inhibitory antibodies against FVIII ≥0.6 BU
The inhibitor rate was to be calculated by dividing number of subjects with neutralizing inhibitors with the number of subjects with at least 50 exposure days. A one-sided, upper 97.5% confidence limit was to be provided based on an exact calculation in the binomial distribution.

Hemostatic effect of N8-GP when used for treatment of bleeding episodes and assessed as: excellent, good, moderate or none
This endpoint was to be summarized and listed. Success was defined as a response of Good or Excellent while failure was defined as Moderate, None or Missing. Success/failure was to be summarized both in total and by location of bleed, by cause of bleed and by country.

Number of bleeding episodes during prophylactic treatment with N8-GP (ABR)
Multiple bleeding locations occurring from the same event (e.g., due to a bicycle accident) or at the same time point were to be counted as one bleeding episode. The ABR of treatment requiring bleeding episodes was to be estimated by a Poisson regression model with log (prophylaxis duration) as offset and estimating over-dispersion by Pearsons scale. The estimated ABR was to be presented together with a 2-sided 95% confidence interval. A sensitivity analysis based on a negative binomial regression model with number of bleeding episodes requiring treatment as the outcome variable, and adjusting for exposure time was also to be performed.

ABR was also to be categorized by subject disposition (such as age group, country, race, and ethnicity) as well as by variables such as treatment regimen, bleeding rate prior to inclusion in this trial and time since last dose.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

A total of 72 subjects were screened for this trial and 68 of these subjects were exposed to N8-GP, thereby comprising the SAS, which was identical to the FAS.

6.3.10.1.1 Demographics

The trial population consisted of male subjects with severe hemophilia A recruited from 36 sites in 15 countries world-wide; of the 36 sites, 35 sites assigned subjects to treatment. The majority of the subjects were ‘White’ (80.9%) followed by ‘Asian’ (7.4%). The remaining part of the trial population was categorized either as ‘Black or African American’ (4.4%), ‘Other’ (2.9%) or not reported (4.4%) (Table 16).

At baseline, the subjects in the 0–5 year age group were characterized by a mean (range) age: 3.0 (1–5) years, height: 99.3 (80.0–120.0) cm and body weight: 16.1 (10.9–23.0) kg. For comparison, the subjects in the 6–11 year age group were of

mean (range) age: 8.9 (6–11) years, height: 136.0 (111.1–160.5) cm and body weight: 34.1 (17.0–60.4) kg.

Table 16 Baseline Demographics and body measurements (FAS)

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Age at baseline (years)			
N	34	34	68
Mean (SD)	3.0 (1.3)	8.9 (1.7)	6.0 (3.3)
Median	3.0	9.0	5.5
Min ; Max	1 ; 5	6 ; 11	1 ; 11
Ethnicity, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Hispanic or Latino	-	3 (8.8)	3 (4.4)
Not Hispanic or Latino	34 (100.0)	30 (88.2)	64 (94.1)
NA	-	1 (2.9)	1 (1.5)
Race, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
White	30 (88.2)	25 (73.5)	55 (80.9)
Black or African American	2 (5.9)	1 (2.9)	3 (4.4)
Asian	1 (2.9)	4 (11.8)	5 (7.4)
Other	1 (2.9)	1 (2.9)	2 (2.9)
NA	-	3 (8.8)	3 (4.4)
Height (cm)			
N	34	34	68
Mean (SD)	99.3 (10.8)	136.0 (13.9)	117.6 (22.3)
Median	100.9	136.0	116.8
Min ; Max	80.0 ; 120.0	111.1 ; 160.5	80.0 ; 160.5
Body weight (kg)			
N	34	34	68
Mean (SD)	16.1 (3.4)	34.1 (11.5)	25.1 (12.4)
Median	16.1	33.8	20.6
Min ; Max	10.9 ; 23.0	17.0 ; 60.4	10.9 ; 60.4

The baseline value for height is the measurement at screening visit 1.
The baseline value for weight is the value from visit 2.
If the visit 2 value for weight was missing, the value from visit 1 was used as baseline.

Source: Adapted from BLA 125671/0; Module 5.3.5.2 NN7088-3885 Main Phase CSR, Table 10-3 and Table 10-4.

6.3.10.1.2 Disease Characterization of the Enrolled Population

All subjects included in the trial were males with severe congenital hemophilia A (FVIII activity <1%), according to medical records. A total of 30 subjects (44.1%) reported history of hemophilia A among relatives. All subjects were PTPs with no history of inhibitors. Mean (range) numbers of EDs to other FVIII products before trial entry were as follows: 207 (51–567) EDs for the 0–5 year age group and 810 (164–1627) EDs for the 6–11 year age group.

Prior to enrolment in the trial, 65 (96%) of the subjects were on prophylactic treatment (61 on rFVIII and 4 on plasma-derived FVIII products). The remaining 3 (4%) subjects were on on-demand treatment. For subjects previously on prophylactic treatment (n=65), mean dose of the previous FVIII product was 33.7 IU/kg and median ABR was 4.0. Previously on-demand subjects (n=3) reported a mean dose of 23.3 IU/kg and a median ABR of 12.

6.3.10.1.3 Subject Disposition

An overview of subject disposition is provided in Table 17.

Table 17 Subject Disposition, Main Phase

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Screened	37	35	72
Exposed	34(100.0)	34(100.0)	68(100.0)
PK patients	15(44.1)	12(35.3)	27(39.7)
Withdrawal	5(14.7)	0(0.0)	5(7.4)
Adverse Events	2(5.9)	0(0.0)	2(2.9)
Other	2(5.9)	0(0.0)	2(2.9)
Withdrawal Criteria	1(2.9)	0(0.0)	1(1.5)
Full analysis set	34(100.0)	34(100.0)	68(100.0)
Safety analysis set	34(100.0)	34(100.0)	68(100.0)
Undergone minor surgery*	2(5.9)	2(5.9)	4(5.9)
Years in trial	15	17	33
EDs in trial	1632	1843	3475

* Minor surgery during trial
The full analysis set and the safety analysis set both consists of all patients exposed to N8-GP
ED: Exposure days

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3885 Main Phase CSR, Table 10-1.

The FAS was evenly distributed between the 0-5 year age-group and the 6-11 year age-group (34 subjects in each). Four subjects were screening failures and were not exposed to N8-GP. A total of 5 subjects, all in the 0–5 year age group, were withdrawn: 2 subjects due to AEs; 1 subject due to withdrawal criteria no. 3 (allergic reaction related to trial product after4 EDs); 2 subjects due to ‘other’ reasons.

6.3.11 Efficacy Analyses

6.3.11.2 Analyses of Secondary Endpoints

Hemostatic effect of N8-GP when used for treatment of bleeding episodes

A summary of hemostatic responses and success rates for all subjects is presented in Table 18. Out of the 70 bleeding episodes in the trial, 67 bleeds were rated, while rating of 3 bleeds were missing. The estimated success rate using the logistic regression model for all bleeds (including missing responses as failure) was 82.1% (95% CI: 70.2; 89.9). The observed the success rate for all bleeds (including missing responses as failure) was 78.6%. The observed success rate appeared similar in the two age groups.

Table 18 Hemostatic response, Main Phase (FAS)

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Number of patients with bleeds, N(%)	19 (55.9)	20 (58.8)	39 (57.4)
Number of bleeds	30	40	70
Haemostatic response, N(%)			
N	30 (100.0)	40 (100.0)	70 (100.0)
Excellent	11 (36.7)	12 (30.0)	23 (32.9)
Good	13 (43.3)	19 (47.5)	32 (45.7)
Moderate	4 (13.3)	7 (17.5)	11 (15.7)
None	1 (3.3)	0 (0.0)	1 (1.4)
Missing	1 (3.3)	2 (5.0)	3 (4.3)
Success/failure			
N	29 (100.0)	38 (100.0)	67 (100.0)
Success	24 (82.8)	31 (81.6)	55 (82.1)
Failure	5 (17.2)	7 (18.4)	12 (17.9)
Success/failure (incl. missing as failure)			
N	30 (100.0)	40 (100.0)	70 (100.0)
Success	24 (80.0)	31 (77.5)	55 (78.6)
Failure	6 (20.0)	9 (22.5)	15 (21.4)
Success rate			
Rate	82.4	81.5	82.1
95% CI	60.6 ; 93.4	68.7 ; 89.8	70.2 ; 89.9
Success rate (incl. missing as failure)			
Rate	80.0	77.4	78.6
95% CI	59.9 ; 91.4	63.4 ; 87.2	67.1 ; 86.9

Analysed using logistic regression accounting for repeated measures within-patient assuming compound symmetry working correlation. Only bleeds treated with N8-GP are included

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3885 Main Phase CSR, Table 11-2.

The hemostatic response was also analyzed by other factors, see Table 19. The total success rate was slightly lower for spontaneous compared with traumatic bleeds. The most predominant location of bleeds was joints (48.0%) followed by skin (18.7%) and muscular (14.7%) bleedings with hemostatic response success rates of 77.8-81.8%. The number of additional N8-GP injections within 8 hours from first injection with no apparent differences observed between the two age groups. The proportion of successfully treated bleeds that were resolved with 1 injection of N8-GP was 62.9%.

Table 19 Hemostatic response -success rates by other factors, Main Phase (FAS)

Factor	Number of bleeds			Total success rate (%)[a]
	0-5 years	6-11 years	Total	
Number of bleeds, N(%)	**30 (100)**	**40 (100)**	**70 (100)**	
Cause of bleed				
Spontaneous	9 (30.0)	10 (25.0)	19 (27.1)	72.6
Traumatic	20 (66.7)	30 (75.0)	50 (71.4)	82.8
After minor surgery	1 (3.3)	-	1 (1.4)	100
Previous treatment				
Prophylaxis	26 (86.7)	40 (100.0)	66 (94.3)	77.2
On-demand	4 (13.3)	-	4 (5.7)	100.0
Time from start of bleed until the first administration of N8-GP				
< 2 hours	15 (50.0)	27 (67.5)	42 (60.0)	83.3
2−4 hours	4 (13.3)	3 (7.5)	7 (10.0)	57.1
> 4 hours	11 (36.7)	10 (25.0)	21 (30.0)	76.2
Number of injections to treat bleed				
1 injection	18 (60.0)	26 (65.0)	44 (62.9)	86.4
2 injections	5 (16.7)	7 (17.5)	12 (17.1)	50.0
3 injections	2 (6.7)	6 (15.0)	8 (11.4)	75.0
4 injections	3 (10.0)	-	3 (4.3)	100.0
5 injections	-	1 (2.5)	1 (1.4)	100.0
6 injections	2 (6.7)	-	2 (2.9)	50.0
Number of bleeds location[b], N(%)	**34 (100)**	**41 (100)**	**75 (100)**	
Location of bleed				
Joint[c]	12 (35.3)	24 (58.5)	36 (48.0)	77.8
Skin	11 (32.4)	3 (7.3)	14 (18.7)	78.6
Muscular	3 (8.8)	8 (19.5)	11 (14.7)	81.8
Mouth/gums/nose	3 (8.8)	1 (2.4)	4 (5.3)	100.0
Stomach	-	1 (2.4)	1 (1.3)	100.0
Other	5 (14.7)	4 (9.8)	9 (12.0)	77.8

No bleeding episodes were classified as severe.

[a] For the total success rate estimates, 'missing' is counted as 'failure'.

[b] A single bleeding episode may occur in multiple locations at the same time.

[c] Target joints are included in joint bleeds. A target joint is defined as three or more bleeds in a period of 6 months in a particular joint.

[a] For the total success rate estimates, 'missing' is counted as 'failure'.

[b] A single bleeding episode may occur in multiple locations at the same time.

[c] Target joints are included in joint bleeds. A target joint is defined as three or more bleeds in a period of 6 months in a particular joint.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3885 Main Phase CSR, Table 11-3.

Number of bleeding episodes during prophylactic treatment with N8-GP (ABR)

A total of 70 bleeds were treated in 39 subjects (57.4%) during the trial. The majority of the bleeds (71.4%) were traumatic, 27.1% were spontaneous bleeds, and a single bleed (1.4%) was due to minor surgery. The most frequent location of bleeds was in a joint, which accounted for 34 (48.6%), divided in 10 joint bleeds in the 0-5 years age-group and 24 joint bleeds in the 6-11 year age-group. All bleeds were classified as mild or moderate. The mean (range) duration of bleeds among the 0-5 years age-group was 53.0 (0.4–209.6) hours compared to 35.2 (1.0–136.2) hours in the 6-11 year age-group. Of the 15 subjects who reported target joint at baseline, 11 subjects did not report any target joint bleeds during the trial, the rest 4 subjects reported 6 bleeding episodes involved a target joint: 2 bleeding episodes in the 0-5 year age-

group (both spontaneous) and 4 bleeding episodes in the 6-11 year age-group (2 spontaneous and 2 traumatic).

Reviewer comment: *Similar to the efficacy analyses in Trial NN7088-3859, non-treatment-requiring bleeding episodes that coincided with regular prophylaxis doses were not included in this trial. The additional efficacy analyses by including the non-treatment required bleeds are included in section 6.3.11.5 of this memo and are reviewed as post-hoc analyses.*

Table 20 shows the summary of the ABR. The Poisson estimate imputed for subjects who withdrew prematurely in the primary analysis was 3.29 (95% CI :2.16; 5.01), 4.28 (95% CI :2.66; 6.89) in the 0-5 year age-group, and 2.30 (95% CI :1.20; 4.40) in the 6-11 year age-group. The median ABR was 1.95 (IQR: 0.00; 2.79) and comparable between the two age-groups. The mean ABR was 3.87 (SD: 9.68) for the 0-5 age group and 2.29 (SD: 2.86) for the 6-11 age group. It was noted that the maximum individual ABR (45.66) was driven by a single subject (number (b) (6) in the 0-5 year age-group who was discontinued early from the trial after 8 EDs due to an adverse event.

Table 20 Annualized bleeding rate, Main Phase (FAS)

	Younger children (0-5 years)	Older children (6-11 years)	Total
Number of patients	34	34	68
Number of patients with bleeds, N(%)	19 (55.9)	20 (58.8)	39 (57.4)
Number of bleeds	30	40	70
Bleeds per patient (min ; max)	0; 4	0; 6	0; 6
Mean treatment period (years)	0.455	0.513	0.484
Individual ABRs			
N	34	34	68
Mean (SD)	3.87 (9.68)	2.29 (2.86)	3.08 (7.13)
Median	1.94	1.97	1.95
Interquartile range	0.00; 2.08	0.00; 3.91	0.00; 2.79
Min ; max	0.00;45.66	0.00;11.53	0.00;45.66
Poisson estimate of ABR	1.94	2.30	2.13
95% CI	1.10; 3.42	1.40; 3.75	1.48; 3.06
Negative binomial estimate of ABR	2.04	2.30	2.18
95% CI	1.29; 3.20	1.54; 3.42	1.61; 2.94
LOCF sensitivity analysis			
Number of patients with less than 30 days of exposure	4	0	4
Number of patients with LOCF	5	0	5
Bleeds per patients (min ; max)	0; 13	0; 6	0; 13
Mean treatment period (years)	0.515	0.513	0.514
Poisson estimate of ABR	4.28	2.30	3.29
95% CI	2.66; 6.89	1.20; 4.40	2.16; 5.01
Negative binomial estimate of ABR	4.33	2.30	3.31
95% CI	2.70; 6.95	1.37; 3.85	2.32; 4.73

Based on a Poisson regression model with age group as a factor allowing over-dispersion and using treatment duration as an offset
A sensitivity analysis was carried out using the negative binomial model with treatment duration as an offset.

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3885 Main Phase CSR, Table 11-4.

Reviewer comment: *The Applicant's primary analysis was based on imputed ABRs as discusses in section 6.1.9 of this memo. Therefore, the "Poisson estimate of ABR"*

following the "LOCF sensitivity analysis" in Table 20 are the planned primary analysis results.

Reviewer comment: *Among the 5 subjects withdrawn, 4 of them had less than 30 days of exposure of N8-GP. Additional analysis was repeated based on observed data without any imputation. The estimated ABR was 2.13 (95% CI :1.48; 3.06), 1.94 (95% CI :1.10; 3.42) in the 0-5 year age-group, and 2.30 (95% CI :1.40; 3.75) in the 6-11 year age-group when no imputation was performed for withdrawn subjects. Sensitivity analyses were also performed by applying a negative binomial regression model as discussed in section 6.1.9 of this memo, the results of all analyses based on this model were consistent with those obtained based on the Poisson model.*

ABRs during the trial NN7088-3885 compared to the ABRs prior to inclusion were assessed for subjects previously on prophylaxis and on-demand treatment (Table 21). Overall, the ABRs reported in the trial NN7088-3885 were lower than the ABRs measured from the last 12 months of exposure to previous FVIII product.

Table 21 Annualized bleeding rate during trial compared to bleeding rate prior to inclusion in Trial NN7088-3885, Main Phase (FAS)

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Previously on prophylactic treatment			
Number of patients	31	34	65
Historical ABRs*			
ABR	4.65	7.94	6.37
ABRs during trial			
ABR	4.06	2.29	3.14
Previously on-demand treatment			
Number of patients	3	0	3
Historical ABRs*			
ABR	16.33	-	16.33
ABRs during trial			
ABR	1.89	-	1.89

* Bleeding rate during last 12 months prior to trial

Source: Original from BLA 125671/0; Module 5.3.5.2 NN7088-3885 Main Phase CSR, Table 11-5.

Consumption of N8-GP per bleeding episode (number of injections and IU/kg)
Of the total 70 bleeds in the trial, 44 (62.9%) were resolved with 1 injection of N8-GP, 12 (17.1%) were resolved with 2 injections; Therefore, 80.0% of bleeds were treated with ≤ 2 injections. The highest number of injections to treat a bleed was 6 injections in 2 bleeding episodes in 0-5 year age group.

The per protocol dose level to be used for treatment of a bleeding episode was 50-75 IU/kg. The mean dose used to treat a bleed was 123 (range: 44.9-436) IU/kg in the 0-5 year age group and 99.0 (range: 49.9-296.4) IU/kg in the 6-11 year age group and 109.3 IU/kg for all bleeds.

6.3.11.4 Dropouts and/or Discontinuations

A total of 5 subjects, all in the 0–5 year age group, were withdrawn: 2 subjects due to AEs; 1 subject due to withdrawal criteria no. 3 (allergic reaction related to trial product after 4 EDs); 2 subjects due to 'other' reasons.

6.3.11.5 Exploratory and Post Hoc Analyses

Analyses by including the non-treatment required bleeds

In addition to the 70 bleeds, 36 bleeds in 7 subjects that didn't require treatment were identified. A total of 43 joint bleeds occurred in the Main part of the trial. Of these, 9 were non-treatment requiring joint bleeds. Hence, the total number of bleeds becomes 106 in 46 subjects. Table 22 summarizes the ABRs by age, treatment regimen, and bleed type for treated bleeds and for all bleeds including the non-treatment required bleeds.

Table 22: Efficacy in pediatric prophylaxis, median and mean ABRs by age, treatment regimen, and bleed type, Main Phase (FAS)

	Prophylaxis Regimen 65 IU/kg twice weekly		
	< 6 years N=34	**6 to < 12 years N=34**	**0 to < 12 years N=68**
Mean treatment duration (years)	0.46	0.51	0.48
Treated bleeds			
# of subjects (%)	19 (56)	20 (59)	39 (57)
# of bleeds	30	40	70
Median ABR (IQR)	1.94 (0.00;2.08)	1.97 (0.00;3.91)	1.95 (0.00;2.79)
Mean ABR (SD)	3.87 (9.68)	2.29 (2.86)	3.08 (7.13)
All Bleeds			
# of subjects (%)	20 (59)	26 (77)	46 (68)
# of bleeds*	41	65	106
Median ABR (IQR)	1.97 (0.00;3.99)	2.02 (1.93;5.99)	2.00 (0.00;4.15)
Mean ABR (SD)	5.00 (11.85)	3.76 (3.59)	4.38 (8.71)
Treated spontaneous bleeds			
# of subjects (%)	6 (18)	7 (21)	13 (19)
# of bleeds	9	10	19
Median ABR (IQR)	0.00 (0.00;0.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)
Mean ABR (SD)	2.09 (7.29)	0.57 (1.47)	1.33 (5.27)
Treated traumatic bleeds			
# of subjects (%)	15 (44)	17 (50)	32 (47)
# of bleeds	20	30	50
Median ABR (IQR)	0.00 (0.00; 2.03)	0.88 (0.00;2.04)	0.00 (0.00;2.03)
Mean ABR (SD)	1.72 (4.00)	1.72 (2.50)	1.72 (3.31)
Treated joint bleeds			
# of subjects (%)	7 (21)	12 (35)	19 (28)
# of bleeds	10	24	34
Median ABR (IQR)	0.00 (0.00;0.00)	0.00 (0.00;2.00)	0.00 (0.00;1.95)
Mean ABR (SD)	1.53 (6.28)	1.37 (2.40)	1.45 (4.72)

*Post-hoc analysis was performed to include non-treatment required bleeds
Mean and Median ABRs are based on observed bleeding episodes without any imputation.
Source: Adapted from BLA 125671/0; Module 2.7.3 Summary of clinical efficacy, multiple tables; BLA amendment 125671/53, Module 1.11.3, multiple tables.

Reviewer comment: *The mean ABRs are increased when the analysis includes non-treatment requiring bleeds in both the prophylaxis and on-demand groups. Although the increases are noticeable, they are within the acceptable range and comparable with other FVIII products, therefore confirm the treatment effect of the 65 IU/kg every twice weekly regimen of the N8-GP for pediatric subjects.*

6.3.12 Safety Analyses

The safety results were evaluated based on all the available data at the submission (Main Phase and Extension Phase).

6.3.12.2 Incidence of Inhibitor

No confirmed FVIII inhibitors developed during the trial. The 1-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 6.7%.

6.3.12.3 Deaths

No deaths occurred during the trial.

6.3.12.4 Nonfatal Serious Adverse Events

A total of 17 SAEs were reported in 15 (22.1%) of the subjects, of which 2 SAEs (preferred term: hemorrhage and hypersensitivity) were evaluated as probably related to trial product by the investigator.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

I verified the primary efficacy and safety results and key second efficacy results for studies NN7088-3859, NN7088-3860 and NN7088-3885. The results summarized below are across these three studies.

On-demand treatment and control of bleeding episodes

There were 1,506 bleeds reported in 171 of 254 subjects across the three studies, and the most common bleed types were joint (65.2%), muscle (14.5%), and subcutaneous (8.9%). Of the 1,506 bleeds, 1,314 (87.2%) were rated excellent or good in their response to ESPEROCT, 167 (11.1%) were moderate, 6 (0.4%) were rated as having no improvement, and for 19 (1.3%) the response to treatment was missing.

Doses used for treatment of bleeding episodes depended on the severity of the bleed. The median dose to treat a bleeding episode was 52 IU/kg across all age groups; 94% of the bleeds were resolved with 1-2 injections of ESPEROCT and 81% were resolved with 1 injection (See Table 23).

Table 23: Summary of efficacy in control of bleeding episodes by age

Age range # of subjects		**< 6 years N=34**	**6 to < 12 years N=34**	**12 to < 18 years N=25**	**≥ 18 years N=161**
# of bleeds		30	40	112	1324
# of injections	1–2	76.7%	82.5%	88.4%	95.5%
	> 2	23.3%	17.5%	11.6%	4.5%
Response to first treatment	Excellent/ Good	80.0%	77.5%	75%	88.7%
	Moderate	13.3%	17.5%	17.9%	10.3%
	None	3.3%	0.0%	0.0%	0.4%
	Missing	3.3%	5.0%	7.1%	0.6%

Source: Adapted from BLA 125671/0; Module 2.7.3 Summary of clinical efficacy, multiple tables.

In the on-demand arm, Main Phase, there were 532 bleeding episodes in 12 out of 12 subjects, treated with 41.0 IU/kg (mean) for mild/moderate bleeds. The overall success rate for treating these bleeds was 92.1%, and 97.0% of all bleeds were treated with 1-2 injections. Including the Extension 1, there were 695 bleeding episodes and 98% of all bleeds were treated with 1-2 injections.

Routine prophylaxis to reduce the frequency of bleeding episodes
During the Main Phase of the adult/adolescent trial, 186 subjects have at least 50 EDs. The mean ABR was estimated by Poisson regression model allowing for over-dispersion. The estimated ABR in the prophylaxis arm was 3.70 (95% CI: 2.94; 4.66). The raw mean ABR was 3.73 (SD: 5.90). The median ABR was 1.33 (IQR: 0.00; 4.61). These estimates are consistent with other FVIII products.
In Extension 1 of the adult/adolescent trial, the efficacy of ESPEROCT by different prophylaxis regimens (75 IU/kg q7D or 50 IU/kg q4D) was assessed in the 55 eligible subjects who agreed to randomization. Thirty-eight subjects were randomized to 75 IU/kg q7D; 28 of this group (74%) completed 6 months on this regimen while 9 subjects resumed the 50 IU/kg q4D regimen. Seventeen subjects were randomized to 50 IU/kg Q4D and 16 (94%) completed Extension 1. On the 75 IU/kg Q7D regimen, 16 subjects had 25 bleeds, with an estimated mean ABR of 3.57 (95% CI: 2.13; 6.00) and median ABR of 0.00 (IQR: 0.00; 2.36). On the 50IU/kg q4D regimen, 8 subjects had 13 bleeds, with an estimated mean ABR of 1.77 (95% CI: 0.59; 5.32) and median ABR of 0.00 (IQR: 0.00; 2.23). The ABR assessment shows that the ABR in subjects who received the q7D regimen was approximately double the ABR in subjects who received the q4D regimen. Therefore, given the number of subjects who required rescue treatment and change to a more frequent dosing and the higher ABR in the q7D regimen, I do not recommend including this dosing regimen in the label due to the increased risk of bleeding under this regimen even for the selected subjects with a lower risk of bleeding (only subjects on prophylaxis with 0−2 bleeds during the last 6 months of the Main Phase had the option of being randomized in Extension 1). Inability to identify characteristics of subjects who are likely to benefit from an every 7-day regimen and in the absence of pre-specified eligibility criteria to define this group of subjects will expose the subjects in a substantial risk of bleeding episodes.

Overall, 68 children below 12 years received prophylactic treatment with ESPEROCT at an average dose of approximately 65 IU/kg twice weekly. The estimated mean ABR imputed for subjects who withdrew prematurely in the primary analysis was 3.29 (95% CI :2.16; 5.01) across all ages, 4.28 (95% CI :2.66; 6.89) in the 0-5 year age-group, and 2.30 (95% CI :1.20; 4.40) in the 6-11 year age-group. The median ABR was 1.95 (IQR: 0.00; 2.79). The raw mean ABR was 3.87 (SD: 9.68) for the 0-5 age group and 2.29 (SD: 2.86) for the 6-11 age group. Of the 68 children, 29 (42.6%) did not experience any bleeding episodes during the Main Phase of the trial. Of the 13 subjects with 17 documented target joints at baseline, 10 subjects (77%) and 14 target joints (82%) did not have any bleeds during the Main Phase of the trial.

Perioperative management of bleeding
The efficacy analysis of ESPEROCT in perioperative management included 45 major surgical procedures performed in 33 adolescent and adult subjects. The procedures

included 15 joint replacements, 9 arthroscopic orthopaedic interventions, 17 other orthopaedic interventions, and 4 non-orthopaedic surgeries. The clinical evaluation of haemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or none. The haemostatic effect of ESPEROCT was rated as "excellent" or "good" in 43 of 45 surgeries (95.6%), while the effect was rated as "moderate" in 2 surgeries (4.4%). No surgery had an outcome rated as "none" or "missing."

Incidence of inhibitors
One previously treated subject developed confirmed neutralizing antibodies to Factor VIII (13.5 BU).

10.2 Conclusions and Recommendations
Based on the results of Trials NN7088-3859, NN7088-3860, and NN7088-3885, adequate statistical evidence supports approval of the proposed indications of: on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in previously treated adults and children with hemophilia A. However, given the number of subjects who required rescue treatment and change to a more frequent dosing and the higher ABR in the q7D prophylaxis regimen, I do not recommend including this dosing regimen in the label due to the increased risk of bleeding under this regimen.