Final Review Memo of Original Application

Application Type	Original Application
STN	125466/0
CBER Received Date	October 16, 2012
PDUFA Goal Date	October 16, 2013
Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	Lisa Faulcon
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Novo Nordisk Inc.
Established Name	Antihemophilic Factor (Recombinant), Plasma/Albumin Free
(Proposed) Trade Name	Novoeight
Pharmacologic Class	Antihemophilic Agent
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder in single-use vials of 250, 500, 1000, 1500, 2000 and 3000 international units for Injectable Solution, Intravenous
Dosing Regimen	The required dosage is determined using the following formula: Dosage Required (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL)
Indication(s) and Intended Population(s)	Indicated in adults and children with hemophilia A for • Control and prevention of bleeding episodes;

	• Perioperative management; • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

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GLOSSARY

ABR	Annualized Bleeding Rate
ADR	Adverse Drug Reaction
BIMO	Bioresearch Monitoring
BU	Bethesda Unit
CHO	Chinese Hamster Ovary
CI	Confidence Interval
eCTD	Electronic Common Technical Document
ED	Exposure Days
GCP	Good Clinical Practices
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IU	International Units
PDD	Preventative Dose Days
PeRC	Pediatric Review Committee
PI	Package Insert
PK	Pharmacokinetic
PTP	Previously Treated Patients
rAHF	Recombinant Antihemophiilc Factor
SAE	Serious Adverse Event
VWF	von Willebrand Factor

1. Executive Summary

STN 125466 is an original biologics license application (BLA) submitted by Novo Nordisk for a recombinant antihemophilic Factor (rAHF) under the trade name Novoeight. Novoeight is a lyophilized, B-domain truncated, recombinant factor VIII (rFVIII) that is produced in a Chinese Hamster Ovary (CHO) cell line without the use of serum or other animal-derived components.

Data from three clinical trials were included for review to demonstrate the efficacy and safety of Novoeight for the following proposed indications for children and adults with hemophilia A:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

The safety and efficacy trials included a pivotal trial of 150 adolescent and adults (trial NN7008-3543), a pediatric trial of 63 children <12 years (NN7008-3545), and an ongoing extension trial of 187 children and adults (NN7008-3568). All were designed as multi-center, open-label, uncontrolled trials with a primary endpoint of incidence of inhibitor formation. Secondary endpoints included annualized bleeding rate (ABR) during the prophylaxis treatment and hemostatic effect on treatment of bleeds for on-demand and perioperative management using a four-point rating scale of excellent, good, moderate and none. Success was defined as a rating of excellent or good. Trials 3543 and 3568 included a study in patients with congenital hemophilia A deficiency

undergoing surgery. The clinical development program for Novoeight also included three pharmacokinetic (PK) studies.

During clinical development, a total of 214 subjects received Novoeight. For routine prophylaxis adults and adolescents were treated with 20-40 international units (IU) of Novoeight per kg body weight every other day or 20-50 IU of Novoeight per kg body weight 3 three times weekly; children under 12 years old were treated with 25-60 IU of Novoeight per kg body weight three times weekly or 25-50 IU of Novoeight per kg body weight every other day. Greater than 80% of subjects were treated with three times weekly regimens.

In the pivotal trial (NN7008-3543), the ABR (bleeds/patient/year) for adolescents and adults was 6.9. When evaluated against historical controls, calculated using data from nine publications (ABR=22), the ABR was reduced by 68%. For the 58 subjects previously treated with on-demand regimens, treatment with Novoeight reduced the ABR from 53 to 7.2, resulting in a >80% reduction in ABR. In the extension trial (NN7008-3568) the ABR was further reduced to 5.3 for adults and 6 for adolescents. In the pediatric trial (NN7008-3545), the ABR for children <12 years was 5.62. Treatment with Novoeight reduced the ABR from 31 to 7.1 for 16 subjects who were previously treated with on-demand regimens. Hemostasis was achieved for 81% of the 499 acute bleeds treated with Novoeight (on-demand therapy) in adolescents and adults, and 92% of the 126 bleeds reported in children. Hemostatic response was 100% successful for perioperative management (during and after surgery) of 10 major, and one minor, surgeries.

The most common adverse drug reaction (ADR) in >0.5% of the 214 subjects treated with Novoeight were injection site reaction (2.3%), increased hepatic enzyme (1.4%) and pyrexia (0.9%). Of the 31 serious adverse events (SAEs) reported, four (hypertension, insomnia and tachycardia reported in one subject and increased hepatic enzymes in another) were assessed as related to Novoeight by the investigator. There was one unrelated death (subdural hemorrhage after an assault) and three AEs (schizophrenia, fatigue lasting 24 hours after every infusion, and increased hepatic enzymes) in three subjects that led to study withdrawal.

No confirmed inhibitors, hypersensitivity/allergic reactions or thromboembolic events were reported for any subject. A transient, low-titer inhibitor of 1.3 Bethesda units (BU) was detected in a twenty-two month old after 20 exposure days (ED), but was not associated with any clinical or adverse findings. A total of 19 subjects were positive for anti-CHO antibodies at some point during the trial; detection was not associated with any clinical adverse events and only two subjects changed from anti-CHO negative to positive.

This submission triggered PREA. The sponsor submitted a pediatric assessment to support the safety and efficacy of Novoeight for use in children 0-16 years of age. In total the safety and efficacy of Novoeight was evaluated in 79 children between 0 and <16 years including 4 from 0 to <2 years, 27 from 2 to <6 years, 32 from 6 to <12 years

and 16 from 12 to <16 years of age. The ABR (95% CI) for the 79 subjects was 4.8 (3.74, 6.15), compared to an ABR of 38 for the 24 pediatric subjects previously treated with on-demand therapy. A total of 244 bleeds in 54 subjects were treated. By cause and site of bleed, 99 (41%) were spontaneous and 142 (58%) were joint bleeds. Hemostatic response was excellent or good for 210 (86%) of the bleeds. No confirmed inhibitors were reported in any subject. These data were presented to Pediatric Review Committee (PeRC), who agreed with the review division that the available data were adequate to establish safety and efficacy in children (0-16 years) with hemophilia A and no additional studies are needed

No post-marketing studies are required for this product. The sponsor has proposed two post-marketing studies in 50 PUPs and an additional 50 PTPs, which is considered post-marketing commitment studies.

Recommendation:
Based on my review of the submitted, data Novoeight appears safe and efficacious in patients with hemophilia A. An approval is recommended.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

HEMOPHILIA A (CONGENITAL FVIII DEFICIENCY):

Hemophilia A is an X-linked coagulation disorder that results from a deficiency or defect in FVIII. It is the most common of the severe, inherited bleeding disorders, affecting 20,000 males in the United States and 1 of every 5,000 male births.[1] Hemophilia A is classified as 'severe (<1%)', 'moderate (1−5%)' or 'mild (>5%)' according to the plasma activity of FVIII. Hemophilia is characterized by recurrent bleeding manifestations that often start at birth with bleeding after circumcision or immunization. Bleeding may occur after minor trauma or small surgical intervention, into skin, joints, mucosa, muscles, gastrointestinal tract or the brain. Primary prophylaxis, i.e., regular infusion of concentrates started after the first joint bleed and/or before the age of two years, is now recognized as first-line treatment in children with severe hemophilia.

The most serious complication of treatment in hemophilia is inhibitor formation, which occurs in up to 30% of patients with severe hemophila A.[2] Large deletions, inversions, and nonsense mutations are associated with the highest risk. The type of mutation also is associated with the severity of hemophilia A.

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

Factor VIII Regulatory History

1 Srivastava A, Brewer AK, Mauser-Bunschoten EP, A *et al*. Guidelines for the management of hemophilia. Haemophilia 2012.
2 Gouw SC, van der Bom JG, Ljung R, *et al*. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013 Jan 17;368(3):231-9.

In the late 1950s and much of the 1960s, fresh frozen plasma (FFP) was the mainstay of treatment for hemophilia A. Cryoprecipitated plasma was introduced in the mid-1960s, and by the late 1960s lyophilized FVIII concentrates from pooled plasma became available. By the 1970s and early 1980s, the use of non–virally inactivated plasma-derived clotting factor concentrates resulted in an epidemic of blood-borne viruses (hepatitis B virus, hepatitis C virus and human immunodeficiency virus). The successful cloning of the factor VIII gene in 1984 allowed for the production of recombinant human FVII (rFVIII). Clinical trials in humans began three years later, and products were widely available after 1994. The advantages of recombinant products includes less viral contamination as compared to plasma-derived products and the potential to produce bioengineered products for improved therapeutics; however, the discordance of labeled units (in vitro) versus recovery in patients (in vivo), differences in laboratory assay methods, and the potential for pathogenic virus from hamster cell cultures were some of the disadvantages.

The first generation licensed rFVIII products was produced in hamster cells and included Recombinate ((b)(4); also claimed by (b)(4) as Recombinate was developed by -----(b)(4)-----, which today is part of (b)(4); approved in 1992) and Helixate FS (Bayer; approved in 1993). These products used media enriched with human or animal plasma proteins for initial cell culture and contained Albumin in the final formulation. For second generation products, such as Helixate FS/Kogenate FS® (Bayer/(b)(4)) and ReFacto® (Wyeth), sucrose was substituted for albumin in the final formulation. Third generation products, such as Advate® (Baxter) and Xyntha® / ReFacto AF® (b)(4) do not contain any human or animal plasma proteins in the purification or final formulation.

Currently Available Treatments

	RECOMBINATE	**KOGENATE FS HELIXATE FS**	**REFACTO**	**ADVATE**	**XYNTHA**
Cell Line	CHO	BHK	CHO	CHO	CHO
FVIII Molecule	Full-length	Full-length	B-domain deleted	Full-length	B-domain deleted
Stabilizer	Human albumin	Sucrose	Sucrose	Trehalose Mannitol	Sucrose Polysorbate 80
Plasma Albumin-Free Method	No	(b)(4)	No	Yes	Yes
Virus Inactivation/ Purification	IA, (b)(4)	IA, IE, SD ----(b)(4)----	----(b)(4)---- ----(b)(4)----	IA, (b)(4), SD ----(b)(4)----	IA, (b)(4), SD nanofiltration
Half-Life	----(b)(4)----------	----(b)(4)----------	----(b)(4)----	----(b)(4)----------	----(b)(4)----------

IA = immunoaffinity

IE= ion exchange

Additional therapeutic options include:

-desmopressin acetate, which is an arginine vasopressin analogue that causes a transient rise in FVIII and von Willebran factor levels (typically used for mild hemophilia)

-antifibrinolytic agents, such as epsilon-aminocaproic acid and tranexamic acid, help preserve the hemostatic plug (typically used prior to dental procedures or to treat mouth or nose bleeds)

2.3 Safety and Efficacy of Pharmacologically Related Products

Pathogen transmission and inhibitor formation are the main safety concerns when treating hemophilia A patients with FVIII replacement therapy. The availability of recombinant FVIII products reduces the risk of pathogen transmission, but not inhibitor development.

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

Novoeight is not currently licensed in any other country.

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

Regulatory Background Information

The following summarizes the regulatory chronology of this BLA:

June 15, 2009	IND submitted (BB-IND 14059)
July 9, 2009	Telecon on study design: immunogenicity testing and surgical study evaluation revised
July 16, 2009	Telecon to discuss deficiencies; study cannot proceed until revisions are submitted and approved by FDA
August 14, 2009	Study may proceed; non-hold items communicated
June 13, 2012	Pre-BLA meeting response: dataset to be arranged by study site
August 3, 2012	Telecon to discuss Pre-BLA responses; clarification on the site-specific data set format requested by sponsor
October 15 2012	BLA submitted

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure. A pediatric assessment was submitted upon request.

3.2 Compliance With Good Clinical Practices And Submission Integrity

In order to assess compliance with GCP and to verify the submitted safety and efficacy data against source documents, an inspection of a few study sites conducting the pivotal

study (3543) was done. CBER Bioresearch Monitoring (BIMO) issued high-priority inspection assignments at two clinical sites in Brazil and two domestic sites:

Study Site Number	Study Site	Location	Number of Subjects
351	Hemorio-Fundarj (State Institute of Hematology)	Rio de Janeiro, Brazil	6
352	University of Campinas	Campinas, Brazil	10
861	Oregon Health & Science University	Portland, Oregon	6
868	University of Iowa Hospitals and Clinics	Iowa City, Iowa	6

The number of study subject enrolled and previous inspection history were among the factors used to select the inspected sites. The inspections focused on specific questions concerning the study protocol and the comparison of data submitted in the BLA to source documents. The BIMO inspections did not reveal any issues that would impact the data submitted in the BLA.

Sponsor-identified Protocol Violations/Deviations

For the pivotal trial there were 397 protocol violations/deviations reported. Most (>200) were related to laboratory samples and assessment deviations that were either missing or taken outside the sampling window. The deviations related to inhibitor testing were largely due to sampling within the 48 hour wash-out period rather than for missing data. Furthermore, some subjects used the "none" category for rating hemostatic response that was not evaluated by the investigator and several subjects from Israel site 101 did not follow protocol in regards to contacting the site for bleeds.

The outlined protocol violation/deviations did not undermine the quality of the trial data and the overall trial conclusions are not invalidated. Sensitivity analyses with data excluded from the Israel site and from data obtained prior to the interim analysis, when it was noted that subjects misunderstood the rating scale, did not change the conclusions about the efficacy of the product.

3.3 Financial Disclosures

Financial certification and disclosure information (Form 3454) have been submitted for both US and Non-US sites. No questions about the integrity of the data were raised.

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

4.1 Chemistry, Manufacturing, and Controls

Novoeight is a human recombinant FVIII with a truncated B domain of 21 amino acid residues. It is a "third generation" FVIII product that is produced in a Chinese Hamster Ovary (CHO) cell line without the use of serum or other animal-derived components.

----------(b)(4)----------.

Novoeight temporarily replaces the missing coagulation FVIII that is required for effective hemostasis. The product was developed to increase the treatment options available for patients with Hemophilia A. Two strengths, 250 IU and 2000 IU, were used in clinical trials.

Selected Specifications for Novoeight

Test parameter	Analytical procedure	Acceptance criteria
Appearance	Visual inspection	Complies
(b)(4)	---(b)(4)---	---(b)(4)---
Identity	---(b)(4)--- ----------	Complies
Potency	Chromogenic substrate assay	---(b)(4)---
Specific activity	Calculated from potency and content	---(b)(4)----- ------
Purity	---(b)(4)---	---(b)(4)---
---(b)(4)---	---(b)(4)---	---(b)(4)---
--------(b)(4)--- ---------- -------	---(b)(4)---	---(b)(4)---

4.2 Assay Validation

The one-stage activated partial thromboplastin time assay (one-stage assay) and a two-stage chromogenic substrate assay (chromogenic assay) were used to determine FVIII activity. Both assays expressed the activity in international units (IU); one IU of FVIII is equivalent to the amount of FVIII in one mL of normal human plasma. The mean FVIII activity was generally higher using the chromogenic assay, as compared to the one-stage assay.

The key validation parameters for the 3 assays are as follows:

Analysis parameter	Anti-CHO antibodies	Anti-murine IgG antibodies	Anti-FVIII neutralizing antibodies
Sensitivity	---------(b)(4)---------	---------(b)(4)---------	--------(b)(4)---------
Cut point	--------(b)(4)---------	--------(b)(4)---------	-----(b)(4)-----
Assay variation	----(b)(4)----	----(b)(4)---	----(b)(4)---

----------(b)(4)----------
----------(b)(4)----------
----------(b)(4)----------

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

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

5.1 Review Strategy

This review focuses on a phase 3 single arm, open label, prospective safety and efficacy trial in adolescents and adults with severe hemophilia A (trial NN7008-3543). In addition, supportive efficacy and safety data from three PK studies, a pediatric trial and an ongoing extension trial were reviewed. The similarities in population and surveillance allowed for an integrated analysis of pooled data from the six clinical trials to evaluate the safety of the product.

REVIEW RESPONSIBILITIES:

Product and Chairperson:	Natalya Ananyeva
	Ze Peng (stability and viral safety)
	Andrey Sarafanov (analytical assays and their validation)
	Zuben Sauna (issues and assays related to immunogenicity)
Clinical:	Lisa Faulcon, MD
DMPQ:	Randa Melhem
Statistician:	Judy Li
ClinPharm:	Iftekhar Mahmood
APLB:	Loan Nguyen
BIMO:	Bhanu Kannan
Pharm/Tox:	La'Nissa Brown
DBSQC:	Karen Campbell
OBE:	Wambui Chege
RPM:	Leigh Pracht

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

The following materials from the submission were considered for the review:

Volume(s)	Information
5.3.3	Reports of human pharmacokinetic (PK) studies
5.3.5	Reports of efficacy and safety studies
5.3.5.24	Case report forms and case report tabulations
1.9.5	Pediatric Assessment

5.3 Table of Studies/Clinical Trials

Tabular Listing of Clinical Trials:

Trial ID (type of study)	Phase	Subjects (n)	Type of Trial	Treatment
NN7008-3522	Phase 1	Enrolled: 23 adolescent or adult	*First human dose trial*	50 IU/kg (single dose) rFVIII FL 50 IU/kg (single dose)
NN7008-	Phase 1	Enrolled: 7 adults	*PK in Japanese*	50 IU/kg (single dose)

3600		(6 analyzed)	*patients*	
NN7008-3893	Phase 1	4 adults	*PK trial (two lots)*	50 IU/kg (single dose)
NN7008-3543	Phase 3	*Total (including subtrial):* 150 adolescent or adults Surgery sub-trial: 9 Pharmacokinetics: 22 patients (same subjects as in Trial 3522)	*Pivotal trial* (Safety and Efficacy)	Routine prophylaxis: 20–40 IU/kg every second day or 20–50 IU/kg three times weekly. PK: 50 IU/kg (single dose) preceded by preventive dosing for 3−6 months
NN7008-3545	Phase 3	*Total:* 63 children <12 years PK: 28	*Pediatric trial* (Safety and Efficacy)	Routine prophylaxis: 25–50 IU/kg every second day or 25–60 IU/kg three times weekly Treatment of bleeds and surgery: investigator's discretion. Pharmacokinetics: 50 IU/kg (single dose). subjects' previous product: 50 IU/kg (single dose)
NN7008-3568	Phase3	*Total (including subtrial):* 188 pediatric, adolescent or adults Surgery sub-trial: 2 patients	*Extension trial* (Safety and Efficacy)	Routine prophylaxis: 20–50 IU/kg every second day or 20–60 IU/kg three times weekly.

Source: Adapted from BLA 125466/0; Clinical Overview V2.5, p.10-11

5.4 Consultations

5.4.1 Advisory Committee Meeting

Pediatric Review Committee (PeRC): Pediatric assessment was reviewed on September 11, 2013; committee agreed with the review division that Novoeight is safe and efficacious for children with hemophilia A.

5.5 Literature Reviewed

1. Aledort LM, Dimichele DM. Inhibitors occur more frequently in African-American and Latino haemophiliacs. Haemophilia.1998 Jan;4(1):68.
2. Berntorp E , Astermark J , Björkman S et al.Consensus perspectives on prophylactic therapy for haemophilia: summary statement. Haemophilia 2003; 9 (Suppl. 1): 1–4.

3. Gouw SC, van der Bom JG, Ljung R, *et al*. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013 Jan 17;368(3):231-9.
4. Gringeri A, Lambert T, Street A, Aledort L; Adolescent/Adult Prophylaxis Expert Working Group of the International Prophylaxis Study Group. Tertiary prophylaxis in adults: is there a rationale? Haemophilia. 2012 Sep;18(5):722-8. doi: 10.1111/j.1365-2516.2012.02843.x. Epub 2012 May 29.
5. Srivastava A, Brewer AK, Mauser-Bunschoten EP, A *et al*. Guidelines for the management of hemophilia. Haemophilia 2012.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Clinical trials 3543 (pivotal trial) and 3545 (pediatric) were used to assess the safety and efficacy of the product in children and adults. Additional data from trial 3568 was used for the integrated analysis to assist in further critical analysis of the data and the conclusions drawn from each trial.

6.1 Trial #1 PIVOTAL TRIAL NN7008-3543

6.1.1 Objectives

Primary:

The primary objective of the trial was to assess the incidence rate of FVIII inhibitors. A positive inhibitor was defined as ≥0.6 BU/mL. The original objective was to assess efficacy, but this objective was changed after feedback from FDA.

Secondary:

- To evaluate the clinical efficacy of Novoeight in bleeding prevention (routine prophylaxis)
- To evaluate the clinical efficacy when treating acute bleeds
- To evaluate the efficacy during surgical procedures and the hemostatic response in the post-surgery period
- To evaluate the safety when used for prevention of bleeds, treatment of acute bleeds, and perioperative management
- Part A only: to describe and compare the pharmacokinetic profile of Novoeight in the subjects who participated in both this trial and NN7008-3522
- To assess changes in patient-reported outcomes

6.1.2 Design Overview

Trial 3543 was the pivotal trial in the clinical development program for Novoeight, and was conducted as a multi-center, multinational, prospective, open-label, uncontrolled study in adolescents and adults (aged 12 to 65 years) with severe Hemophilia A. The subjects were recruited at 48 sites in 15 countries. All subjects were in a non-bleeding state. The trial included three parts: Part A included subjects who completed the pharmacokinetic trial (Trial 3522); Part B included all other subjects; Part C included subjects from Part A or Part B undergoing surgical procedures. The treatment period was 20-28 weeks per subject.

Reviewer Comment: The design of the pivotal trial is sufficient to support the indication of treatment of bleeding in patients with hemophilia.

6.1.3 Population

Important Eligibility Criteria

Inclusion Criteria

- Male patients with the diagnosis of severe (FVIII≤1%) hemophilia A from age 12 to 65 years.
- Willing to undergo a bleeding preventive treatment of 75 dose days.
- Non-bleeding state
- Documented history of at least 150 exposure days to any other FVIII products.
- No detectable inhibitors to FVIII (≥0.6 BU) and no history of inhibitors.
- Immunocompetent, and if HIV positive: CD4 lymphocytes >200/µl and viral load <200 particles/µl.

Exclusion Criteria

- Patients who received immune modulating medication or tolerance induction regimens.
- Platelet count <50,000 platelets/µL; ALT > 4 times the upper limit of normal reference range; creatinine levels 50% above normal level.
- Severe current hepatic dysfunction or severe hepatic disease during the last 12 months.
- Congenital or acquired coagulation disorders other than hemophilia A.
- Use of anticoagulants or platelet inhibitors including NSAIDs one week prior to first administration of trial product.
- The receipt of any investigational drug within 30 days prior to administration of trial product except for patients who completed Trial 3522.
- Any disease or condition which, judged by the investigator, could imply a potential hazard to the patient, interfere with the trial participation or trial outcome.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Prophylaxis

Subjects in part A and B received either 20-40 IU/kg body weight (BW) every other day or 20-50 IU/kg three times per week of Novoeight for at least 75 preventative dose days. A total of 125/150 (83%) subjects were treated with the three times per week regimen. One subject (----(b)(6)----) switched to an every other day regimen.

On-demand

Subjects received 20-50 IU/kg for mild/moderate bleeds and doses of up to 200 IU/kg per day for up to 14 days could be used at the discretion of the investigator for treatment of a severe bleed.

Surgery

Doses were calculated based on the recovery of Novoeight that was measured in the individual subject at Pre-surgery Day prior to the surgical procedure.

6.1.5 Directions for Use

Novoeight is supplied as a powder for administration by intravenous injection after reconstitution. A total of 35 Novoeight related medication errors were recorded, and were related to incorrect dosing, including intentional overdosing before pharmacokinetic wash-out periods and calculation errors. A Human Factors consultative review identified that the subjects were not drawn to the critical task of drawing out a specified volume of the reconstituted drug into the syringe (less than the full contents of the reconstituted solution). Revisions to the instructions for use sections were made to address the potential for dosing errors.

Reviewer comment: In clinical practice, doses are rounded to the nearest vial, which may often result in overdosing with no clinical adverse effect.

6.1.6 Sites and Centers

The subjects were recruited at 48 sites in 15 countries: Brazil (2 sites), Croatia (2 sites), Germany (4 sites), Israel (1 site), Italy (2 sites), Japan (8 sites), Malaysia (1 site), Russian Federation (1 site), Republic of Serbia (5 sites), Spain (2 sites), Switzerland (1 site), Taiwan (1 site), Turkey (5 sites), the UK (3 sites) and the US (10 sites).

6.1.7 Surveillance/Monitoring

In addition to an Institutional Review Boards/Independent Ethics Committee (IRB/IEC), a Novo Nordisk internal safety committee was in place to evaluate safety and PK data for all subjects in NN7008-3522 before the subjects were included in NN7008-3543. A patient diary, which was used to record bleeds and preventive treatment, was reviewed by the investigator at each visit. All procedures and assessments, including severe bleeds, were recorded by the investigator in the electronic case report form (eCRF).

Safety assessments anti-HCP and anti-murine antibodies, AEs, physical examinations, vital signs, electrocardiogram, laboratory assessments (hematology, biochemistry, coagulation factors and parameters), as well as viral monitoring that included testing for HIV-1 and 2, HBV, and HCV viruses.

Inhibitors were measured at these specified time points:

- Part A: screening/baseline, 12 ±3 preventative dose days (PDD) 28 ±3 PDDs, 90 to 180 days after initial visit, 56±3PDD, 70±3PDD and 75±3PDD
- Part B: screening, baseline, 12 ±3 PPDs, 28 ±3 PDDs, 42±3 PDDs, 56±3PDD, 70±3PDD and 75±3PDD
- Part C: pre-Surgery, last day of recovery

PDD was defined as one day for a subject in a non-bleeding state of receiving one dose of prophylactic treatment (dose level 20-40 IU/kg BW or 20-50 IU/kg BW every other day or three times per week, respectively) and was used for the purpose of scheduling visits in this trial. Exposure days (ED) are all the days the subject has been exposed to trial product when used for treatment of bleeds, prevention of bleeds and treatment of bleeds during surgery and was used for reporting purposes and for inhibitor rate calculations.

Reviewer Comment: The current testing schedule of every 4-5 weeks during study participation is sufficient to capture the development of all clinically relevant FVIII inhibitors.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint
The primary endpoint is the incidence rate of factor VIII inhibitors (≥0.6 BU/mL). Acceptable safety with regard to inhibitors (study success) was to be concluded if the upper bound of 97.5% confidence interval (CI) of the incidence rate of FVIII inhibitors is below 6.8%.

Efficacy Endpoints
Treatment of bleeds

- Hemostatic effect using a four-point rate scale of excellent, good, moderate, or none. Success was defined as receiving a rating of "excellent" or "good." If the hemostatic response was rated as "moderate" or "none", the treatment was considered a failure.
- The number of infusions required per bleeding episode
- The time to control of bleeding after the first dose
- Actual consumption

Prevention of bleeds

- Annualized bleeding rate
- Total consumption per patient per month
- Actual consumption (IU/kg/month)

Reviewer Comment: The protocol stated that the efficacy endpoint for prevention of bleeds will be the "average number of bleeds per month"; however, the ABR was reported instead since it is the standard way of reporting the bleeding rates (p. 27/40 of the SAP, "changes from the protocol"). This change was acceptable, as it does not alter the final conclusions of the trial.

Perioperative management

- Hemostatic effect intra- and post-operatively using a four-point rate scale of excellent, good, moderate, or none. Success was defined as receiving a rating of "excellent" or "good."
- Actual consumption between Day 1 and Day 7 and from Day 8 to return to preventative treatment regimen

Safety Endpoints

- Frequency of adverse events (AEs) and serious AEs (SAEs)
- Vital signs (blood pressure, pulse, temperature, and respiratory rate).
- Clinical laboratory tests
- Transmission of viruses

Pharmacokinetic Endpoints

- Incremental recovery of FVIII
- AUC
- Terminal half-life
- Clearance

6.1.9 Statistical Considerations & Statistical Analysis Plan
See Dr. Judy Li's memo for full review.

All descriptions and analyses of safety and efficacy were done on the full analysis set (FAS). The rate of inhibitor formation was calculated for subjects in Part A and B by the dividing the number of subjects with inhibitors by the number of subjects with a minimum of 50 exposures plus any subjects with less than 50 exposures with positive inhibitors. The incidence rate was reported together with a one-sided 97.5% upper confidence limit. The incidence rate of inhibitors was assessed separately for subjects who underwent surgery.

The evaluation of data was based on descriptive statistics. The ABR was estimated by a Poisson model, and presented with a 95% confidence interval. Additional analyses include assessment of the ABR by cause (spontaneous, traumatic), site, and severity of bleed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Full Analysis Set included "all dosed subjects with data after dosing."

6.1.10.1.1 Demographics

Table 2. Demographics and baseline characteristics

	Part A	Part C	Total (Part A and Part B)
Number of patients	22	9	150
Age (years)			
N	22	9	150
Mean (SD)	24 (7.88)	25 (6.53)	28 (11.79)
Median	22	25	25
Min ; Max	13 ; 54	14 ; 36	12 ; 60
Ethnicity, N (%)			
N	22 (100.0)	9 (100.0)	150 (100.0)
Hispanic Or Latino	0 (0.0)	0 (0.0)	25 (16.7)
Not Hispanic Or Latino	22 (100.0)	9 (100.0)	125 (83.3)
Race, N (%)			
N	22 (100.0)	9 (100.0)	150 (100.0)
White	21 (95.5)	9 (100.0)	121 (80.7)
Black Or African American	0 (0.0)	0 (0.0)	3 (2.0)
Asian	1 (4.5)	0 (0.0)	20 (13.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	6 (4.0)

Source: Original BLA 125466/0; Clinical Study Synopsis V5.3.5.2.2, p.5

The enrolled population inadequately represents the broader population targeted by the proposed indication. It is comprised of an ethnic population (80% Caucasians) that is at lower risk for inhibitor formation. Published literature suggests that inhibitors may occur more frequently in African Americans and Latinos.[3] Due to the low enrollment of Hispanic/Latino and Black/African-American subjects it will difficult to do a meaningful subgroup analysis to determine if the inhibitor rate differs in these populations.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline Disease Characteristics

Previous Prophylaxis Regimen[a] (n, (%))	91 (61)
Average Months on Prophylaxis (range)	79 (2-480)
Average prophylactic dose (range)	25 IU/kg (7-63)
Previous Recombinant Treatment (n, (%))	69 (46)

a. includes subjects who had been on both prophylaxis and on-demand
Source: Original BLA 125466/0; Demographic Data Listing V5.3.5.2.19, section

16.2.4.6

6.1.10.1.3 Subject Disposition

Table 1. Patient disposition

	Part A N (%)	Part C N (%)	Total (Part A and Part B) N (%)
Screened			172
Dosed	22 (100.0)	9 (100.0)	150 (100.0)
Withdrawal	0 (0.0)	0 (0.0)	4 (2.7)
Adverse event	0 (0.0)	0 (0.0)	1 (0.7)
Initiation of other treatment*	0 (0.0)	0 (0.0)	1 (0.7)
Other	0 (0.0)	0 (0.0)	2 (1.3)
Lost to follow up	0 (0.0)	0 (0.0)	1 (0.7)
Enrolled by mistake**	0 (0.0)	0 (0.0)	1 (0.7)
Completed trial	22 (100.0)	9 (100.0)	146 (97.3)
Full Analysis Set***	22 (100.0)	9 (100.0)	150 (100.0)

Source: Original BLA 125466/0; Clinical Study Synopsis V5.3.5.2.2, p.2

The screen failure rate of 13% and attrition rate of 3% are acceptable.

6.1.11 Efficacy Analyses

No formal per-protocol analysis was proposed for secondary endpoints. All main descriptions and analyses of efficacy were based on the FAS. The ABR was estimated by

3 Aledort LM, Dimichele DM. Inhibitors occur more frequently in African-American and Latino haemophiliacs. Haemophilia.1998 Jan;4(1):68.

a Poisson model allowing for overdispersion, which was agreed upon during the IND phase.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was safety, and is described in the safety section.

6.1.11.2 Analyses of Secondary Endpoints

Annualized Bleeding Rate (bleeds/patient/year)

The hemostatic efficacy of prophylaxis with Novoeight was evaluated against historical controls. Of the 150 subjects dosed, a total of 142 subjects had at least 75 EDs, and 148 (97%) had at least 50 EDs. The median dose per prophylactic infusion was 20.8 IU/kg (mean 24.4 IU/kg; range 12.8-97.4 IU/kg).

The ABR for the 150 subjects was estimated by a Poisson model allowing for overdispersion and compared to a calculated ABR for historical controls. A mean ABR for historical controls was estimated from nine publications. The bleeding rate from each trial was weighted by the number of subjects in the trial. The calculated mean ABR was 22 for historical controls treated with on-demand therapy, and was estimated as 6.9 for subjects treated with routine prophylaxis with Novoeight. This is a 68% reduction the bleeding rate.

The sponsor reports an ABR (95% CI) of 6.5 (5.3, 7.97) for subjects treated with Novoeight; however, this rate only included bleeds that required treatment. This results in an underestimate of the true ABR. The more accurate ABR (95% CI) that is inclusive of all bleeds is similar at 6.9 (5.67, 8.41). The ABR is lower if you only consider bleeds that occur within 48 hours after the last preventative dose. Considering the variation in bleeding rates observed between subjects, it reasonable to consider the median ABR, which is 4.08 for this trial.

The ABR for the year prior to study enrollment was calculated based on the average number of bleeds per month that was reported by each subject previously treated with on-demand therapy (n=58). The calculated mean ABR was 53 (median 36; range 12-216), as compared to an ABR (95% CI) of 7.2 (5.29, 9.92) after treatment with Novoeight. For subjects previously treated with on-demand therapy, treatment with Novoeight resulted in a greater than 80% reduction in their ABR.

Reviewer Comment: This is a single arm study which does not allow for a formal comparison of the bleeding rates between prophylaxis and on-demand treatment regimens. Improvements in the clinical management of patients with Hemophilia A have resulted in many patients, and mostly all children, being managed on prophylactic regimens. As a result, the number of subjects eligible for enrollment into on-demand regimens is reduced. Instead, the use of historical data as a comparator to determine efficacy of a prophylactic regimen has been allowed by FDA. It is important to note that in this trial, the ABR for the year prior to study enrollment that was calculated for each subject was based on self-reported monthly

bleeds rates for each subject. These data are therefore subject to recall bias and may not accurately reflect the true historical bleeding rate for this population.

Hemostatic Efficacy
The hemostatic response after treatment with Novoeight for acute bleeding episodes was evaluated on a four-point scale as excellent, good, moderate or none. A total of 499 acute bleeds were reported in 105 subjects. The median dose for treatment of a bleed was 27.2 IU/kg/dose (range 9.8 to 61.1 IU/kg).

A total of 499 acute bleeds were reported in 105 subjects. The median dose for treatment of a bleed was 27.2 IU/kg/dose (range 9.8 to 61.1 IU/kg). By site and causality for all bleeds, 373 (75%) were joint bleeds, 332 (66%) were spontaneous, 124 (25%) traumatic, and 43 (9%) were of unknown cause. Ninety percent were of mild severity. Sixty-seven percent (67%) of the 46 severe bleeds occurred in the joint.

A total of 357 bleeds (71%) were treated with one infusion, 89 (18%) were treated with two infusions and the remaining 11% required more than three infusions. The mean duration from start to stop of a bleed was 16.4 hours ranging from 15 minutes to 304 hours. One subject (---(b)(6)---) required 26 infusions to treat stop a muscle bleed caused by a trauma. The duration of the bleed was 304 hours and the hemostatic response was rated as good. The hemostatic response was rated as excellent or good for 403 (80.8%) of the bleeds. Of the 140 bleeds rated as excellent, 136 (97%) were treated with one or two infusions; four were treated with three infusions. There was no treatment effect for 2.4% of the bleeds, and an additional 4.4% were not rated.

Reviewer Comment: A success rate was not pre-specified in the protocol; however, a response rate of >80% is clinically significant. The success rate of 80.8% is lower than the sponsor's report of 84.5%, which was calculated with missing data excluded. The protocol did not specify how missing data would be handled, therefore in my analysis all missing data were considered failures.

Perioperative Management
Hemostasis was successful in all of the nine surgeries (eight major and one minor) that were done in nine subjects. From Day 1 to Day 7 of the surgery, the mean consumption was 432 IU/kg (61.6 IU/kg/day) and from Day 8 and until the subjects returned to the preventive regimen, the mean consumption was 399 IU/kg. Total doses of up to 153 IU/kg BW were given on surgery Day 1 (range 60-153 IU/kg). On average, blood loss was not significantly more than anticipated (236 mL anticipated; 258 actual).

6.1.11.3 Subpopulation Analyses

Annualized Bleeding Rate
The ABR was not clinically significantly different between adolescents and adults.

Hemostatic Efficacy
The success rate for treatment of bleeds in the adolescent population was lower at 71.6%.

6.1.11.4 Dropouts and/or Discontinuations

A total of 4 subjects (3 adults and 1 adolescent) withdrew from the trial for the following reasons:

- --(b)(6)--: adverse event (fatigue for 24 hours after infusion)
- --(b)(6)--: treatment with another FVIII containing product
- --(b)(6)--: lost to follow-up
- --(b)(6)--: considered ineligible after it was determined that the adolescent subject had a history of a positive inhibitor test of 1 BU at another medical facility

Reviewer Comment: Withdrawals from clinical trials are ubiquitous; the number of subjects who were withdrawn and the reasons for their withdrawal does not undermine the data or the conclusions drawn about the clinical trial.

6.1.11.5 Exploratory and Post Hoc Analyses

Site of Bleed

Success rates were >80% for various location of bleeds, such as joint (n=373; 80.4%) and muscular (n=25; 88%) bleeds. In the assessment of eight left elbow joint bleeds (all rated mild/moderate) in five subjects, all were successfully treated with one dose of Novoeight using similar doses (range of 21.6 to 38.3 IU/kg/dose). For treatments of gastrointestinal bleeds (n=3), the success rate was only 67%. Of the three severe gastrointestinal bleeds (GI) treated with Novoeight, two of the three bleeds required a single infusion of Novoeight and received a hemostatic efficacy rating of good. The doses used to treat were similar for these two cases (26.5 compared to 29.7 IU/kg). The third case required five infusions and took a week to resolve. This hemostatic efficacy was rated as "moderate" and the subject received a total of 197.3 IU/kg of product over that five day period. Additional data are needed to adequately assess the hemostatic efficacy of Novoeight to treat GI bleeds

Number of Infusions

A total of 813 doses were used to treat 499 bleeds (range 1 to 26 infusions). A total of 446 (89%) required one (71%) or two infusions (18%). One subject (-(b)(6)-) was treated with 26 infusions for a severe muscle bleed that started on August 22, 2010 and resolved on August 23, 2010. The rating for this event was good.

6.1.12 Safety Analyses

6.1.12.1 Methods

Exposure to Novoeight

Of the 150 subjects exposed to Novoeight, 142 subjects had at least 75 EDs and 148 had at least 50 EDs; four subjects completed the trial without 75 exposure days (ED) as a result of miscalculation of exposure days at the investigational sites (three subjects) or failure to return the final two diaries (EDs were only counted for this patient up until Visit 7).

The majority of the subjects (82.7%) followed the three times per week dosing schedule, 16.7% were dosed every other day and one patient (<1%) changed dosing schedule from three times per week to every second day. The average number of doses used for prevention, treatment of bleeds and surgery was 86.4 (range 11-213).

6.1.12.2 Overview of Adverse Events

Primary Endpoint
The trial achieved its primary endpoint; 97.5% upper CI for the inhibitor rate of zero was 1.77%.

Treatment Emergent Adverse Events
The majority of TEAE, herein after referred to as AEs, occurred in the prophylactic treatment group. Ten reported SAEs occurred in eight subjects. An additional five AEs were considered severe:

- elevated blood glucose
- presence of glucose in the urine
- sinusitis
- arthropathy
- depression (previous history of mental illness)

Reviewer's comment: The quantity of sucrose per mL of reconstituted factor is 1.5mg, therefore IV administration of the sucrose contained in Novoeight should not result in significant glucosuria at recommended doses.

In general, the most common AE (>5%) was related to dosing (18/150 [12%]), followed by headache (15/150 [10%]) and nasopharyngitis (12 /150 [8%]). The most frequently reported causally-related adverse reactions were incorrect dose administered (2%) and increased hepatic enzymes (1.3%).

Table 12–2 Overview of adverse events – safety analysis set

	Part A and Part B N (%) E	Part C N (%) E	Total N (%) E
Number of patients	150	9	150
All Adverse Events	99(66.0) 222	3(33.3) 3	100(66.7) 225
Serious Adverse Events	7(4.7) 9	0(0.0) 0	7(4.7) 9
Severe Adverse Events	7(4.7) 8	0(0.0) 0	7(4.7) 8
Adverse Events Probably or Possibly Related to Trial Product	11(7.3) 17	0(0.0) 0	11(7.3) 17
Adverse Events Leading to withdrawal	1(0.7) 1	0(0.0) 0	1(0.7) 1

Adverse events reported during surgeries are displayed in part C, adverse events reported outside surgeries are displayed in part A and part B.
All adverse events reported during the trial are displayed in total
N: Number of patients with adverse event
%: Percentage of patients with adverse event
E: Number of adverse events

Source: Original BLA 125466/0; Clinical Study Report V5.3.5.2., p.134

6.1.12.3 Deaths

No deaths occurred during the trial.

6.1.12.4 Nonfatal Serious Adverse Events

SAEs were reported as follows:

Table 12–5 Listing of serious adverse events – safety analysis set

Patient number	Trial Part	Age	Preferred term	ED*	Relation-ship	Severity	Outcome
(b)(6)	Part A	20	Melaena	59	Unlikely	Severe	Recovered
	Part A	24	Upper gastrointestinal haemorrhage	85	Unlikely	Severe	Recovered
	Part B	26	Hypertension	28	Possible	Moderate	Recovered
			Sinus tachycardia	28	Possible	Moderate	Recovered
			Insomnia	28	Possible	Moderate	Recovered
	Part B	58	Melaena	11	Unlikely	Mild	Recovered
	Part A	21	Road traffic accident	16	Unlikely	Severe	Recovered
	Part B	13	Fall	66	Unlikely	Moderate	Recovered
	Part B	36	Hepatic enzyme increased	84	Probable	Moderate	Recovering

*ED:Number of Exposure days before onset of event.
The relationship was judged by the investigator.

Source: Original BLA 125466/0; Clinical Study Report V5.3.5.2., p.140

Not included in tables 12-2 and 12-5 (above) is an SAE of suicide attempt in a subject (---(b)(6)---) with a known history of depression.

Reviewer Comment: The relationship between the hepatic enzyme increase and the product is unlikely to be related. The subject had concomitant disease of HIV and chronic hepatitis C that likely resulted in the elevations. A liver biopsy showed findings consistent with chronic hepatitis, including lobular inflammation and mild portal fibrosis. Even upon de-challenge elevations in the enzymes persisted, and even increased again three months after Novoeight was discontinued.

6.1.12.5 Adverse Events of Special Interest (AESI)

The ongoing safety concerns are hypersensitivity and allergic reactions, thromboembolic events and inhibitor development. There were no hypersensitivity reactions, thromboembolic events or inhibitor formation during the trial.

Medication errors associated with Novoeight administration were considered as medical events of special interest. A total of 22 medication errors were recorded in 18 (12%) subjects, including two that occurred in adolescents. Most were related to the administration of higher doses than planned. Subject ---(b)(6)--- received five times the planned dose (100 IU.kg BW) without any clinical adverse events.

6.1.12.6 Clinical Test Results

Increased levels of hepatic enzymes were reported for three subjects (----------(b)(6)----------. All of the subjects had underlying conditions of HCV and/or HIV positive

at screening: patient number ---(b)(6)--- was both HCV and HIV positive at screening, patient number ---(b)(6)--- was HCV positive and HIV negative at screening and patient number --(b)(6)-- was HCV reactive and HIV positive at screening. Abnormal liver tests are an uncommon and labeled side effect for replacement FVIII products, and occurred in 2% of this trial population.

No subjects developed new anti-murine antibodies; five subjects had positive anti-murine antibodies and eight had anti-HCP antibodies prior to dosing.

List of Subjects with Positive anti-CHO antibodies

Subject ID	**Age (yrs)**	**Previous Regimen**	**Previous Treatment**	**Test Results by Visit**				
				1	2b	4	7	9
-(b)(6)-	17	Prophylaxis	Plasma	Pos	Neg	Pos	Pos	Pos
-(b)(6)-	14	Prophylaxis	Plasma	Pos	Pos	Pos	Pos	Neg
-(b)(6)-	22	Prophylaxis	Recombinant	Pos	Pos	Pos	Pos	Pos
-(b)(6)-	23	Prophylaxis	Plasma	Neg	Neg	Neg	Pos	Neg
-(b)(6)-	14	On-Demand	Plasma	Neg	Neg	Pos	Pos	Neg
-(b)(6)-	12	On-Demand	Plasma	Pos	Pos	Neg	Neg	Neg
-(b)(6)-	37	Prophylaxis	Recombinant	Pos	Neg	Pos	Pos	Pos
-(b)(6)-	28	Prophylaxis	Recombinant	Pos	Pos	Pos	Pos	Neg
-(b)(6)-	44	On-Demand	Plasma	Pos	Neg	Pos	Neg	Pos
-(b)(6)-	16	On-Demand	Plasma	Pos	Pos	Pos	Pos	Pos

Source: Adapted from Original BLA 125466/0; Clinical Trial Report V5.3.5.2., Appendix 16.2.4

All of the subjects that tested positive for anti-CHO antibodies during the trial were also positive at baseline. There is no evidence to suggest that the presence of these antibodies correlate with poor clinical outcomes. Titer results were not determined due to low level of antibodies just above the assay cut point. Optical density data from confirmatory assays provide a semi-quantitative measure and do not suggest that repeated exposure results in increased titer formation.

6.1.12.7 Dropouts and/or Discontinuations
One non-serious adverse event of fatigue lasting for 24 hours after every infusion led to withdrawal of the patient (---(b)(6)---). Fatigue/malaise has been identified during post-approval use of other recombinant FVIII products. In addition, one subject withdrew from the continuation trial due to increased hepatic enzymes noted during the participation in this trial.

6.2 Trial #2
PEDIATRIC TRIAL NN7008-3543

6.2.1 Objectives

Primary Objective:
To evaluate the safety of Novoeight in pediatric PTPs <12 years of age with hemophilia A

Secondary Objectives:

- To evaluate pharmacokinetics of Novoeight
- To evaluate hemostatic efficacy
- To assess and compare patient-reported outcomes

6.2.2 Design Overview

This was a multi-center, multinational, prospective, open-label, uncontrolled trial safety, efficacy and PK trial in children with a history of at least 50 EDs with their previous FVIII product. All subjects were treated with prophylactic treatment until each reached at least 50 EDs (18-22 weeks). The trial was designed to include at least 50 completed subjects in two age cohorts: one cohort including 25 small children (0 to < 6 years) and one cohort including 25 older children (6 to < 12 years). The first subjects were enrolled in order to ensure that at least 13 subjects in each age group completed the PK part of the trial.

6.2.3 Population

Important Eligibility Criteria

Inclusion Criteria

- Male patients with the diagnosis of severe (FVIII≤1%) hemophilia A
- Age <12 years and body weight ≥11 kg
- Non-bleeding state
- Documented history of at least 50 exposure days to any other FVIII products
- No FVIII inhibitors at screening and documented negative inhibitor test within first 50 EDs
- HIV seronegative or if HIV seropositive to have a CD4+ lymphocyte count >200/μL

Exclusion Criteria

- Patients who received immune modulating medication or tolerance induction regimens.
- Severe hepatic and/or renal dysfunction
- Documented diagnosis of obesity
- Surgery (exceptions were port placement, dental extractions, and minor, uncomplicated emergent procedures).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Prophylaxis

25-50 IU/kg every other day or 25-60 IU/kg three times weekly

On-demand

Max of 150 IU/kg BW; aim for trough level ≥0.50 IU/mL (investigator discretion)

Dose determined as follows:

Required units = BW (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Surgery
Max of 150 IU/kg BW; aim for trough level ≥0.50 IU/mL

PK
50 IU/kg ±5 IU/kg

6.2.6 Sites and Centers
The country distribution was as follows (number of actively recruiting sites per country in parenthesis): Brazil (3), Italy (1), Lithuania (1), Macedonia (1), Malaysia (1), Poland (2), Russia (2), Serbia (1), Taiwan (1), Turkey (3) and the US (10).

6.2.7 Surveillance/Monitoring

An internal safety committee performed ongoing safety surveillance. Safety assessments include anti-HCP antibodies, AEs, physical examinations, vital signs, and laboratory assessments.

Inhibitors were measured approximately every 28 ±4 days, except for visit 4 which was scheduled 10-14 EDs after Visit 3.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint
The primary endpoint was the incidence rate of Factor VIII inhibitors (≥0.6 BU/mL). Adequate safety with regard to inhibitors (study success) was to be concluded if the upper bound of 97.5% confidence interval of the incidence rate of FVIII inhibitors was below 10.7%.

Reviewer Comment: This inhibitor rate was based on allowing the development of one inhibitor in fifty subjects.

Efficacy Endpoints
Treatment of bleeds

- Hemostatic effect using a four-point ordinal scale of excellent, good, moderate, or none (defined on page 72 of 116 of the protocol). If the hemostatic response was rated as moderate or none, the treatment was considered a failure.
- The number of infusions required per bleeding episode
- The time to control of bleeding after the first dose

Prevention of bleeds

- Frequency of bleeds (average bleeds per month reported as ABR)

Safety Endpoints

- Frequency of AEs and SAEs

- Vital signs (blood pressure, pulse, temperature, and respiratory rate).
- Clinical laboratory tests

Pharmacokinetic Endpoints

- Incremental recovery of FVIII
- AUC
- Terminal half-life
- Clearance

6.2.9 Statistical Considerations & Statistical Analysis Plan
See Dr. Judy Li's memo for full review.

All main descriptions and analyses of safety, efficacy and PK data were based on the FAS. The safety analysis set was identical to the FAS. The primary endpoint was incidence rate of FVIII inhibitors and a one-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. Success for the primary endpoint was concluded if the upper one-sided 97.5% confidence limit was below 10.7% (based on one out of the planned 50 subjects).

The ABR was estimated by cause of bleed (spontaneous, traumatic or other) using a Poisson model allowing for overdispersion. Evaluation of efficacy during treatment of bleeds was based on a four-point rating scale and reported using descriptive statistics.

6.2.10 Study Population and Disposition
Of the 63 subject exposed to Novoeight, 59 (28 children <6 years and 31 children 6 to <12 years) had at least 50 EDs; 60 completed the study.

6.2.10.1 Populations Enrolled/Analyzed

The Full Analysis Set included all dosed subjects with data after dosing.

6.2.10.1.1 Demographics

Table 1. Demographics and baseline characteristics

	Small children (0 - <6 years)	Older children (6 - <12 years)	Total
Number of patients	31	32	63
Age (years)			
N	31	32	63
Mean (SD)	3.65 (1.40)	8.44 (1.85)	6.08 (2.91)
Median	4.00	9.00	6.00
Min ; Max	1.00 ; 5.00	6.00 ; 11.00	1.00 ; 11.00
Ethnicity, N (%)			
N	31 (100.0)	32 (100.0)	63 (100.0)
Hispanic Or Latino	11 (35.5)	5 (15.6)	16 (25.4)
Not Hispanic Or Latino	20 (64.5)	27 (84.4)	47 (74.6)
Race, N (%)			
N	31 (100.0)	32 (100.0)	63 (100.0)
White	27 (87.1)	26 (81.3)	53 (84.1)
Asian	2 (6.5)	4 (12.5)	6 (9.5)
Other	2 (6.5)	2 (6.3)	4 (6.3)

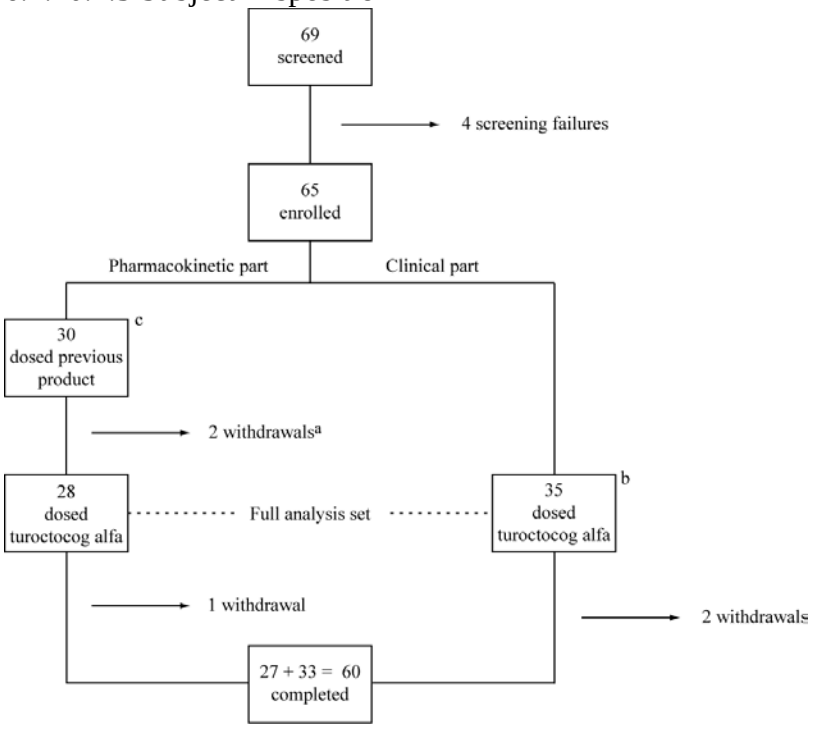
Source: Original BLA 125466/0; Clinical Trial Synopsis V 5.3.5.2.2, page 4

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline Disease Characteristics

Previous Prophylaxis Regimen[a] (n, (%))	48 (76)
Average Months on Prophylaxis (range)	34 (1-110)
Average prophylactic dose IU/kg (range)	36.6 (15-250)
Previous Recombinant Treatment n, (%)	32 (53)

6.2.10.1.3 Subject Disposition



a: Two patients (numbers ----------(b)(6)---------) had PK assessments of previous FVIII product only. These two patients are not included in the full analysis set.
b: Data from patient number ---(b)(6)--- was excluded from the PK results due to wrong storage of the PK samples. This patient was included in the clinical part of the trial.
c: Only 26 of these patients were included in the PK assessment of previous FVIII product. The following patients were not included in the PK assessment of previous product: patient numbers --------(b)(6)---------- where withdrawn (a), patient number --(b)(6)-- had very sparse historical PK data with previous product and patient number --(b)(6)-- had information about previous FVIII product from a local laboratory only.
Source: Original BLA 125466/0; Clinical Trial Synopsis V 5.3.5.2.2, page 2

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint is described in the safety section.

6.2.11.2 Analyses of Secondary Endpoints

Annualized Bleeding Rate

The ABR was (95% CI) is 5.62 (4.16, 7.59). The median ABR was 3.31 for this trial. The ABR was the same even with the exclusion of bleeds that occurred more than 72 hours out from the last preventive dose. For the subjects previously treated with on-demand regimens, the mean ABR was reduced from 31 to an estimated ABR (95% CI) of 7.1 (4.26, 11.72).

Hemostatic Efficacy

The majority of the 126 reported bleeds that were reported in 41 subjects was caused by trauma, was mild/moderate in severity, and located in the joint. The hemostatic response was rated as excellent or good for 116 (92.1%) of the bleeds. There was no treatment effect for two (1.6%) of the bleeds, including one traumatic bleed of the left hand in a 7-year old (---(b)(6)---) who required eight infusions. Three additional bleeds required more than two infusions but were rated as excellent or good, including hemarthrosis in a 9 year old (---(b)(6)---) that required three infusions but still gave a rating of excellent. A total of three of the bleeds (2.4%) had no rating recorded. Of the 126 reported bleeds, 102 (81.0%) were stopped with one infusion and eighteen (14.3%) were stopped with 2 infusions.

Two minor surgeries (dental extraction and central line removal) in two subjects were rated as excellent.

PK

Weight normalized clearance and half-life were similar amongst all age groups. As expected, clearance decreased with subject age and was slowest in young children <2 years. In children <6 years and 6-12 years, the clearance of was approximately 62% and 45% of adult clearance. These differences provide justification for the higher proposed dosing for pediatric subjects.

6.2.11.4 Dropouts and/or Discontinuations

Two subjects were withdrawn before dosing with Novoeight because of a history of a positive inhibitor and difficulty with the planned monitoring schedule. A total of three subjects withdrew from the trial after dosing for the following reasons:

--(b)(6)--: 1 year old; withdrawn after three and a half months due to poor compliance

--(b)(6)--: 7 years of age; after five and a half months

--(b)(6)--: 1 year of age; after two months for use of another FVIII product

Reviewer Comment: The number of subjects who were withdrawn and the reasons for their withdrawal does not undermine the data or the conclusions drawn about the clinical trial.

6.2.11.5 Exploratory and Post Hoc Analyses

Consumption

Comparison of Recommended and Average Doses (IU/kg BW)

Regimen	Recommended	Average Dose (IU/kg; range)
Prophylaxis	25-60[a]	36.8 (3.2 – 73.9)
On-demand	Investigator discretion	40.4 (25.5-193.8)

a. Subjects received either 25-50 IU/kg every second day or 25-60 IU/kg three times weekly.

The majority of the subjects (75%) started the trial on the three times per week dosing schedule. Fifteen subjects (24%) had reported changes to their dosing schedule during the trial.

6.2.12 Safety Analyses

6.2.12.1 Methods

Exposure to Novoeight
All evaluations of safety were based on the FAS. Of the 63 subjects that were exposed to Novoeight, 59 (28 small children and 31 older children) had at least 50 exposure days.

6.2.12.2 Overview of Adverse Events

Primary Endpoint
The 97.5% upper CI for the inhibitor rate of zero was 6.06%, which met the primary endpoint since it was below 10.7%.

One patient had a positive FVIII inhibitor test (1.3 BU) at Visit 4 but the result of a second separately drawn sample was negative (drawn within two weeks); therefore the definition of confirmed FVIII inhibitor was not met.

Adverse Events
A total of 86 AEs were reported for 32 (51%) of subjects. All were mild/moderate in severity. The most common (>5%) AE was related to dosing (5/63 [8%]), nasopharyngitis (5/63 [8%]) and upper respiratory tract infection (5/63 [8%]).

Two events (incorrect dose administered and contusion) in one subject (1.6%) were evaluated by the investigator to be possibly related to Novoeight. Both events were non-serious and were mild or moderate severity.

Six mild and unlikely related AEs were reported in the two subjects who underwent minor surgery.

6.12.3 Deaths

No deaths occurred during the trial.

6.2.12.4 Nonfatal Serious Adverse Events

Three reported SAEs occurred in three subjects (4.8%). All three were unlikely related to the product and were reported as follows:

Table 12–5 Listing of serious adverse events – safety analysis set

Patient number	Age	Preferred term	ED*	Relation-ship	Severity	Outcome
(b)(6)	4	Soft tissue injury	104	Unlikely	Moderate	Recovered
	3	Gastroenteritis viral	82	Unlikely	Moderate	Recovered
	7	Device related infection	199	Unlikely	Mild	Recovered

*ED:Number of Exposure days before onset of event.
Age refers to the patient's age at baseline and not at the time of the event
The relationship was judged by the investigator.
Source: Original BLA 125466/0; Clinical Study Report V5.3.5.2., p.140

6.2.12.5 Adverse Events of Special Interest (AESI)

The safety concerns are hypersensitivity and allergic reactions, thromboembolic events and inhibitor development. There were no drug-related hypersensitivity reactions, thromboembolic events or confirmed inhibitor formation during the trial.

One subject (--(b)(6)--) had a positive anti-FVIII antibody test, which was not confirmed. This occurred in a 22 month old Brazilian boy with a history of 50 EDs using various plasma-derived FVIII products, including Optivate, Octavi, Hemofil and Fanhdi Grifols. The subject was started on 40 IU/kg BW three times weekly prophylaxis on July 18, 2011. A blood sample taken on August 22, 2011 (Visit 4) was reported as 1.3 BU, with FVIII activity of 0.539 and 0.807 IU/mL by OS and chromogenic assay, respectively. Repeat testing was done on September 2, 2011 (less than two weeks later) and was <0.6 BU. The subject was withdrawn on September 12, 2011 due to treatment with another FVIII product.

Reviewer Comment: This finding of a low-titer, transient inhibitor is included in the label. It is important to note that the level of FVIII activity and the lack of associated clinical symptoms suggest that this low-titer inhibitor was not clinically significant.

Medication errors were considered as medical events of special interest. A total of five medication errors were recorded in four subjects, including one that was associated with a contusion. There were no clinical adverse event relating to under- or overdosing.

No subjects developed new anti-murine antibodies. Two subjects changed anti-CHO antibody status from negative to positive:

List of Subjects with Positive anti-CHO antibodies

Subject ID	**Age (yrs)**	**Test Results By Visit**	
		2	8
-(b)(6)-	5	Neg	Pos
-(b)(6)-	3	Pos	Pos

-(b)(6)-	1	Pos	Pos
-(b)(6)-	5	Pos	Pos
-(b)(6)-	6	Neg	Pos
-(b)(6)-	7	Pos	Pos
-(b)(6)-	11	Pos	Neg
-(b)(6)-	2	Pos	Neg
-(b)(6)-	6	Pos	-

Source: Adapted from Original BLA 125466/0; Clinical Trial Report V5.3.5.2., Appendix 16.2.4

6.2.12.6 Clinical Test Results

Results on safety laboratory parameters and other safety-related examinations did not indicate clinically relevant changes as a result of Novoeight administration.

6.2.12.7 Dropouts and/or Discontinuations

No subjects were withdrawn due to adverse events.

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated analysis of data from the following studies was used to further critically evaluate the results and conclusions drawn about the efficacy of the product. Preventive in the table below is for prophylactic regimen.

Table 4-1 Overview of trials providing evidence of clinical efficacy

Trial ID	Number of dosed patients	Treatment
Trial 3543	*Total trial (including sub-trial):* 150 adolescent or adult patients with severe haemophilia A. *Surgery sub-trial:* 9 adolescent or adult patients with severe haemophilia A	*Preventive* 20−50 IU/kg 3 times weekly or 20−40 IU/kg every second day *Treatment of acute bleeds* At the investigator's discretion aiming for a FVIII recovery >0.5 IU/mL. *Surgery* At the investigator's discretion aiming for a FVIII trough activity of >0.5 IU/mL. The doses should be according to local standard practice at the treatment centre.
Trial 3545	63 paediatric patients (below 12 years of age) with severe haemophilia A	*Preventive* 25−60 IU/kg 3 times weekly or 25−50 IU/kg every second day *Treatment of acute bleeds* At the investigator's discretion aiming for a FVIII recovery >0.5 IU/mL
Trial 3568	55 paediatric, 23 adolescent and 109 adult patients with severe haemophilia A (as of the cut-off date of 21 November 2011)	*Preventive* 20−60 IU/kg 3 times weekly or 20−50 IU/kg every second day *Treatment of acute bleeds* At the investigator's discretion aiming for a FVIII recovery >0.5 IU/mL *Surgery* At the investigator's discretion aiming for a FVIII trough activity of >0.5 IU/mL. The doses should be according to local standard practice at the treatment centre

Source: Original BLA 125466/0; Clinical Overview V2.5, p.20

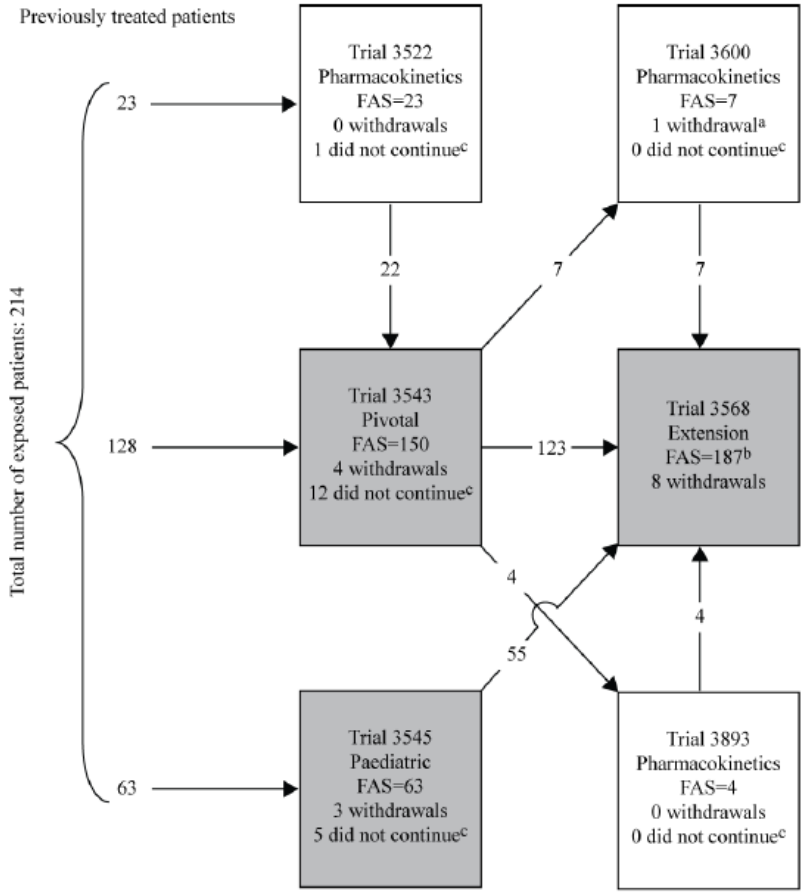
7.1 Indication #1

Control and prevention of bleeding episodes in adults, adolescents and children (0 – 12) with hemophilia A

7.1.1 Methods of Integration

The three safety and efficacy trials were designed as multi-center, open-label, uncontrolled trials; the secondary objectives to support this indication were the same. Pooled pediatric data was assessed separately.

7.1.3 Subject Disposition



a) One patient was withdrawn from Trial 3600, and was allowed to continue in Trial 3568
b) 189 patients entered Trial 3568, but at the cut-off date (21 November 2011), one patient had dropped out prior to dosing and another patient did not yet have any information on treatment. Therefore FAS=187
c) One patient did not continue from Trial 3522 to Trial 3543. 12 patients did not continue from Trial 3543 to Trial 3568. 5 patients did not continue from Trial 3545 to Trial 3568

Source: Original BLA 125466/0; Summary of Clinical Efficacy V2.7.3, p.28.

Reviewer Comment: The number of subjects lost to follow up was low; the withdrawal rate for each trial was less than 10%, and were mostly due to the use of non-study drug. This does not have an impact on the efficacy analyses and final

conclusions. A total of 8% of subjects from trial 3543 (12/150) and 3545 (5/63) did not continue into trial 3568, and one subject only participated in the PK study. No subjects were excluded from the analysis.

7.1.4 Analysis of Primary Endpoint(s)
The primary endpoint for all trials was inhibitor formation.

7.1.5 Analysis of Secondary Endpoint(s)
For all studies, the hemostatic response rate was assessed using the same four-point scale and a rating of excellent or good was considered a successful treatment response.

Information about type of dose (preventive or treatment of bleed) was obtained from the subjects' diary and reviewed at each visit, which can be impacted by recall bias and invented data. Furthermore, the adjudication process can result in inaccurate interpretation of missing data. For instance, if the type of dose regimen was ticked as treatment of a bleed in the patient's diary between two preventive doses, but no bleed was reported, then the dose was re-classified as preventive. This could underestimate the number of actual bleeds treated if the re-classification was incorrect. The number of recorded cases in which this occurred appears to be low and does not change the outcomes of the trials.

A total of 991 bleeds were reported in 158 subjects. Most were spontaneous bleeds into the joint. Approximately 84% were treated successfully and 91% required one or two infusions. The hemostatic effect on treatment of bleeds appeared to be consistent across all trials and age groups. All bleeding categories (minor, moderate and major) were treated during the trials. The success rate for the treatment of GI bleeds remained low at only 60%; however, only five bleeds were assessed which represents less than one percent of the total bleeds observed. Additional observations are necessary to draw meaningful conclusions about the ability of this product to treat GI bleeds.

7.1.8 Persistence of Efficacy

The hemostatic effect was unrelated to the number of months that the subjects were treated.

7.1.11 Efficacy Conclusions
This product is effective for the control and prevention of bleeding episodes in patients with hemophilia A. The recommended doses in the label are acceptable.

7.2 Indication #2
Perioperative management of patients with hemophilia A

7.2.2 Demographics and Baseline Characteristics
A total of 11 surgeries were performed in 11 subjects of which 10 were major surgeries and 1 was minor. The majority of the subjects were adults (mean age was 27 years; range 14 to 54 years). Subjects were from Israel (2 subjects), Italy (1 patient), Serbia (2

subjects), Switzerland (1 patient), Turkey (1 patient), the UK (1 patient) and the US (3 subjects). The surgery indications included arthropathy and chronic pain in left knee (n=1), synovitis (n=1), semi-impacted tooth and removal of tooth root (n=1), arthropathy (n=4), circumcision (n=1), recurrent hemarthrosis (n=1), pain in left ankle (n=1), and poly-trauma (n=1). In addition, 3 'other surgical procedures' were performed in 3 subjects and 2 were related to tooth extractions and one was a removal of a periumbilicial abscess.

7.2.5 Analysis of Secondary Endpoint(s)

Hemostasis was successful in all the surgeries. For all eleven surgeries, the mean total consumption from Day 1 to Day 7 was 418 IU/kg (range 192-728), which equates to an average of 60 IU/kg per day (range 27 to 104 IU/kg per day for the first seven days).

Reviewer Comment: The majority of the surgical data obtained is from adults; however, the efficacy of the product in this setting can be extrapolated to adolescents and children as the overall hemostatic response rate is similar. The doses recommended in the draft PI is based on recommendations from the EMA, and is consistent with the doses used in this trial.

7.2.6 Other Endpoints

The mean hemoglobin level before surgery was 9.53 mmol/L ranging from 8.32 to10.35 mmol/L. The mean hemoglobin levels 1 hour and 24 hours after surgery were 9.4% and 16.2% lower, respectively. These values may be influenced by changes in the total fluid balance of the body. There were no significant differences between anticipated and actual blood loss.

7.2.11 Efficacy Conclusions

This product is effective for perioperative management. Based on daily consumption and efficacy response, the recommended dose proposed in the draft PI is appropriate.

7.3 Indication #3

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults, adolescents and children

7.3.2 Demographics and Baseline Characteristics

During the trials, the majority of the subjects (>80%) were treated with a three times per week regimen. A total of 68 subjects were treated with Novoeight for at least 12 months, of which three were children <6 years, four were older children (6 to <12 years), eight were adolescents and 53 were adults. The mean age was 24.2 years, ranging from 3 to 55 years.

7.3.5 Analysis of Secondary Endpoint(s)

The ABR was similar for the subjects treated for 12 months when compared to the ABR for the total trial population.

The ABR for the year prior to study enrollment was calculated for subjects previously treated with on-demand therapy based on the average number of bleeds per month that was reported by each subject. For the 58 subjects enrolled in the pivotal and extension trials that were previously treated with on-demand regimens only, the calculated mean ABR was 53 (median 36; range 12-216). When these subjects switched to prophylaxis treatment with Novoeight, the estimated ABR was 5.3 for adults and 6 for adolescents, resulting in a greater than 80% reduction in their ABR. For those subjects previously treated with at least 12 months of prophylaxis (n=85 at the cut-off date of 21 November 2011), the ABR was reduced from 6.1 to 3.86. For those treated with on-demand therapy (n=73) the ABR was reduced from 47 to 5.53.

7.3.11 Efficacy Conclusions

The data supports the efficacy of the prophylaxis regimen.

8. INTEGRATED OVERVIEW OF SAFETY

The safety concerns for this product are hypersensitivity and allergic reactions, thromboembolic events, and inhibitor development. Data from the three efficacy and safety trials and from the three PK studies were pooled to allow for an integrated prioritized review of safety topics.

8.2 Safety Database

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

As of September 1, 2012 (120-days safety update) the total number of exposed subjects was 214, including 180 who have been treated for greater than one year.
These subjects had a total of 54,957 EDs during prevention and for treatment of bleeds. As expected, most of the exposure was observed in Trials 3543 (pivotal), 3545 (pediatric) and 3568 (extension). The mean age was 21.5 years, with a range of one to sixty years.

The mean age for 14 subjects undergoing surgery was 28.4 years (range 14–55 years). These subjects had a total of 222 EDs to Novoeight (average of 17 EDs per patient).

8.2.3 Categorization of Adverse Events
All serious and non-serious adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

8.4 Safety Results

There were 783 AEs reported in 179 subjects (2.29/subject); 30 were evaluated as related to the product by the investigator. The majority of the AEs were mild or moderate; 28 severe AEs occurred in 22 subjects and were all unrelated to the product. Six AEs reported during surgery were unrelated to the product, including hemorrhage in subject --(b)(6)-- and hematemesis in subject --(b)(6)--.

8.4.1 Deaths
As of the 1 May 2012 one death was reported. A Malaysian 27-year-old patient (subject -(b)(6)-) died in Trial 3568 (extension study) after suffering severe brain trauma from an assault. On admission the patient was unconsciousness with a Glasgow coma scale 7. A computerized tomography (CT) scan revealed a right-sided frontotemporal parietal subdural hemorrhage with midline shift and cerebral edema. The patient underwent an emergency (right) decompressive craniotomy with evacuation of the hematoma and was covered with Novoeight prior to surgery and until he was declared dead two days later.

8.4.2 Nonfatal Serious Adverse Events
All SAEs occurred during the safety and efficacy trials. There were 31 nonfatal SAEs, of which four (hypertension, insomnia and tachycardia in subject and increased hepatic enzymes in another) were considered causally related by the investigator.

Mild hypertension and sinus tachycardia were detected in one patient who also reported insomnia for two days. The subject was admitted for observation, and blood pressure and heart rate normalized without medical intervention. This subject later experienced the fatal subdural hemorrhage described above.

The subject with increased hepatic enzymes had a history of HCV, HIV, and a mildly elevated aspartate aminotransferase at baseline. Elevations in hepatic enzymes were noted after 84 EDs, and persisted after Novoeight was discontinued. A liver biopsy showed findings consistent with chronic hepatitis, including lobular inflammation and mild portal fibrosis. This clinical reviewer finds that the elevations in hepatic enzymes were unlikely to be related to Novoeight.

A review of the submissions to the IND revealed that there was a report of a serious, unexpected adverse event of renal vein thrombosis in a 19 year old male (subject -(b)(6)-) that was submitted to the IND. The diagnosis was changed after the sponsor re-evaluated medical records. The radiologist for the diagnostic ultrasound was contacted and concluded that the findings were suggestive of renal hemorrhage rather than thrombosis.

8.4.3 Study Dropouts/Discontinuations
There were four AEs of fatigue, schizophrenia, (fatal) subdural hemorrhage and increased hepatic enzymes that resulted in withdrawal. No new safety concerns have been identified.

8.4.4 Common Adverse Events
The most frequently reported AE (>6%) in the pooled safety analysis set were headache (22 [10.3%]) and nasopharyngitis (22[10.3%]), followed by incorrect dose (19[8.9%]), arthralgia (13[6.1]) and pyrexia (13[6.1]). Nineteen subjects (8.9%) had suspected (causally-related) AEs.

The most common ADRs were injection site reactions (2.3%), increased hepatic enzymes (1.4%), and pyrexia (0.9%). In addition, four subjects (1.87) had suspected (causally-related) AEs related to incorrect dose administration.

8.4.5 Clinical Test Results
A total of 18 adverse events of increased hepatic parameters (defined as alanine aminotransferase, aspartate aminotransferase, bilirubin conjugated, blood alkaline phosphatase, total bilirubin, hyperbilirubinaemia, gamma-glutamyltransferase and 'hepatic enzymes increased') were recorded for 10 subjects. The majority (8/10=80%) of these subjects were positive for hepatitis C, which most likely explains the increased values. Most of these events (14/18=78%) were unlikely related to trial product. Four of these events were recorded by the investigator as probably or possibly related to trial product and occurred in three subjects (----------(b)(6)----------). After review of the data, only subject (-(b)(6)-) did not have an alternative reason for the elevations.

One subject in the continuation trial and one in PK trial 3893 experienced mildly elevated blood glucose levels. The quantity of sucrose per mL of reconstituted factor should not affect blood glucose levels at recommended doses.

8.4.8 Adverse Events of Special Interest
As noted above one subject had a positive anti FVIII antibody test of 1.3 BU that was not confirmed with subsequent testing.

8.5 Additional Safety Evaluations
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
A total of 35 medication errors were recorded, including three overdoses. No symptoms of overdosing were reported in any clinical trial. A Human Factors consultative review identified issues with the instructions for drawing out specified volumes of the reconstituted drug into syringes, and advised a revision of the 'Instructions for Use.'

8.5.8 Immunogenicity (Safety)
No confirmed inhibitors were reported; however, there was one inhibitor of 1.3 BU that was detected but not confirmed in a pediatric subject. The development of one inhibitor in 214 subjects would still result in the upper bound of 97.5% confidence interval of the incidence rate of Factor VIII inhibitors being below 6.8%, and therefore would meet FDA's current standard for inhibitor assessment. The one-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero for the pooled data was 1.77%.

A total of 19 subjects were positive for anti-CHO antibodies at some point during the trial. Of these, 2 subjects changed from anti-CHO negative to anti-CHO positive. The clinical importance of these findings remains unclear. Further review of the data is needed to determine continued treatment increases the antibody titers and whether a positive antibody test affects clinical outcomes.

8.6 Safety Conclusions
The product appears well-tolerated. No new safety concerns were identified.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.3 Pediatric Use and PREA Considerations

PREA was triggered as a new indication was being sought.

The safety and efficacy of Novoeight in children was established in a multi-center, multi-national, prospective, open-label, uncontrolled safety, efficacy and PK trial in children <12 years of age. A total of 63 subjects were enrolled and treated with at least one dose of Novoeight, including 31 children 0 to <6 years of age and 32 children 6 to <12 years. The median age was 6 years (range 1-11 years). All were males with severe (FVIII≤1%) hemophilia A and had > 50 EDs with previous FVIII products. The majority of the subjects were White (84%); the second-largest group was Asian (10%). A total of 48 subjects (76%) were previously treated with prophylactic regimens for an average of 34 months (range 1-110 months). Sixty-nine (69) subjects (46%) were previously treated with recombinant FVIII products.

Pediatric Trial Characteristics

Study type	Safety/Efficacy/PK
Study Design	Prospective, open-label, uncontrolled
Ages Studied	0 to <12 years of age
Subject (n) Small children (0 - <6) Older children (6 - <12)	63 31 32
Centers (n)	26
Countries (n)	11
Countries (centers, n)	Brazil (3), Italy (1), Lithuania (1), Macedonia (1), Malaysia (1), Poland (2), Russia (2), Serbia (1), Taiwan (1), Turkey (3) and the US (10)
Race, N (%) White Asian Other	63 53 (84%) 6 (10%) 4 (6%)

Subjects were treated with prophylactic regimens of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly for 18-22 weeks (at least 50 EDs). The primary endpoint was the incidence rate of FVIII inhibitors (≥0.6 BU/mL) measured at 10-14 EDs and approximately every 28 days. Secondary efficacy endpoints included ABR, hemostatic effect using a four-point scale of "excellent", "good", "moderate", or "none", number of infusions required per bleeding episode, and time to control of bleeding after the first dose. All main descriptions and analyses of safety, efficacy and PK data were based on the FAS.

RESULTS

- There were no confirmed neutralizing antibodies to FVIII. One 22- month old child developed a transient low-titer inhibitor (1.3 BU) after 15 exposure days. In vivo recovery was normal for this child and no clinical adverse findings were observed.
- Hemostatic efficacy for the treatment of acute bleeds in 41 subjects was successful for 116/126 (92%) of bleeds treated. A total of 102/126 (81.0%) were stopped with one infusion and eighteen (14.3%) were stopped with 2 infusions.
- Hemostatic efficacy for two minor surgeries (dental extraction and central line removal) in two subjects was rated as "excellent".
- The ABR (95% CI) was 5.62 (4.16, 7.59) bleeds/patient/year, with an average prophylactic dose of 36.8 IU/kg (range 3.2-73.9 IU/kg). The mean ABR for the twelve months prior to trial enrollment for subjects previously treated with on-demand therapy was 34.
- The pharmacokinetic parameters were comparable between younger (0 to < 6 years) and older (6 to < 12 years) children. The mean clearance of Novoeight in younger and older children was 67% and 34% higher (based on per kg body weight) than in adults (3.74 mL/h/kg) when using the clotting assay, and 60% and 29% higher than in adults (2.87 mL/h/kg) when using the chromogenic substrate assay. As clearance (based on per kg body weight) is higher in children, higher or more frequent dosing may be needed.

PeRC ASSESSMENT

The data from the pediatric trial and pediatric patients in the pivotal trial were presented to the Pediatric Review Committee (PeRC) on September 11th, 2013. Between the pivotal and pediatric trials, the safety and efficacy of Novoeight was evaluated in 79 children between 0 and <16 years, including 4 from 0 to <2 years, 27 from 2 to <6 years, 32 from 6 to <12 years, and 16 from 12 to <16 years of age. No confirmed inhibitors were reported in any subject. Hemostatic response in 54 subjects was excellent or good for 210/244 (86%) of bleeds. The ABR (95% CI) for the 79 subjects was 4.8 (3.74, 6.15). Based on these data, PeRC agreed with the review decision that that Novoeight is safe and efficacious for children with hemophilia A. These findings are accurately reflected in the Pediatric Use section of the Package Insert.

10. CONCLUSIONS

Novoeight appears reasonably safe and likely to provide therapeutic benefit to patients with hemophilia A. No reports of hypersensitivity/allergic reactions, thromboembolic events or confirmed inhibitor development were reported. Hemostasis was successfully achieved in the treatment of acute bleeds and during surgery. Prophylaxis reduced the ABR for subjects previously treated with on-demand therapy by greater than fifty percent.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table below.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a hereditary bleeding disorder characterized by recurrent bleeding, which if left untreated bleeds lead to chronic arthropathy, muscular atrophy and deformities. • Treatment of bleeds may delay these complications, but does not prevent it. • Primary prophylaxis with regular FVIII injections initiated at an early age is becoming the standard of care	• Hemophilia A is a hereditary, life-threatening disease • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Clinical Benefit	• Three trials were submitted: a pivotal trial in 150 adults and adolescents, a pediatric study in 63 children and an extension trial that includes 188 previously treated subjects. Efficacy was demonstrated in all populations for on-demand and routine prophylaxis therapies. No new safety concerns were identified. One pediatric subject developed a low-titer, transient inhibitor which was not associated with any clinical complications. • Insubstantial efficacy was noted in the treatment of gastrointestinal bleeds; however, the study was underpowered to full assess the efficacy of treatment for these bleeds.	• The evidence for clinical benefit is compelling.
Risk	• The most substantial risks of treatment with Novoeight are allergic reactions and development of FVIII inhibitors. No confirmed inhibitors or allergic reactions were noted during the trial; however, the study may have been underpowered to adequately identify these potential risks. • A few injection site reactions were noted during the trial. However, all were mild in severity, and resolved relatively quickly and without sequelae. • No other safety signals were apparent.	• All the evidence indicates that Novoeight was well tolerated.
Risk Management	• The most substantial risks of treatment with Novoeight are allergic reactions and development of FVIII inhibitors. There • No other safety signals were apparent.	• The package insert and the current pharmacovigilance plan, including the post-marketing studies, would be adequate to manage the risks

11.2 Risk-Benefit Summary and Assessment

The benefit of treatment by Novoeight outweighs the risks; the risk-benefit profile is favorable.

11.3 Discussion of Regulatory Options

The need for postmarketing requirement studies to further characterize the risk of inhibitor was considered for this product. The identification and characterization of risk factors for inhibitor formation requires an improved understanding of how patient-specific and treatment-related factors work together to influence inhibitory antibody production. Pre-market studies are limited in their ability to identify risk factors because most studies are underpowered and are limited to only previously treated patients (PTPs) who do not have a history of inhibitor formation. The larger hemophilia community that will be exposed to the product after licensure, including minimally treated (MTPs) and PUPs as well as patients undergoing surgery and/or switching regimens, are often not included in the pre-market studies. Large prospective post-marketing surveillance studies that include the patient population at large and designed to actively monitor and evaluate the risk factors for inhibitors are important for further characterization of the risk of inhibitor formation.

The data submitted includes a data for 214 PTPs, of which 79 were pediatric subjects <16 years and 11 were subjects who underwent surgery. In addition, the sponsor has proposed two postmarketing commitment studies that will evaluate the risk of inhibitors in PUPS and further characterize the risk in PTPs after prolonged exposure. Both studies propose to include 50 subjects, which is sufficient for the PUPs study and may be sufficient for the PTP study for this product since we have data for more than 200 PTPs.

11.4 Recommendations on Regulatory Actions

Approval is recommended.

11.5 Labeling Review and Recommendations

NovoNordisk requested a proprietary name review on October 16, 2012 for the tradename Novoeight/ Plasma/Albumin Free. The proposed proprietary name of the product, Novoeight, was determined to be acceptable. A copy of an acceptable Full Prescribing Information (FPI) is attached as Appendix 1. Carton and container labels submitted to BLA were considered acceptable.

The FPI was reviewed by the BLA committee, including Advertising Promotional Labeling Branch, during the labeling review meetings on July 2, 2013 and August 9, 2013. Initial comments regarding product labeling comprehension were conveyed to Novo Nordisk on August 15, 2013. Baxter provided a response on August 26, 2013. Additional comments were sent to Baxter on Monday, September 9, 2013.

11.6 Recommendations on Postmarketing Actions

The sponsor has submitted protocols for two postmarketing studies in their pharmacovigilence plan: an observational trial of 50 subjects for a minimum of 100 EDs over four years and a trial in at least 50 PUPs who will be treated for a minimum of 50

EDs over 3.5 years, which will serve as postmarketing commitment studies. Inhibitor and genotype testing will be done.

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