Consolidated Protocol no.3

Including Substantial Protocol Amendment no. 1, 5 and 6 (Applicable for all countries) to

Study ID: NN7025-3601

Prospective Observational Study on NovoSeven® Room Temperature Stable (VII25) in Patients with
Haemophilia A or B

Non-interventional study

Protocol originator:

Haem, ClinOps 4

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# Table of Contents

Table of Contents .................................................................................................................................................................................. 2  
List of figures and tables ................................................................................................................................................................................ 4  
1 List of abbreviations .................................................................................................................................................................................. 5  
2 Summary ........................................................................................................................................................................................................... 7  
3 Flow Chart ..................................................................................................................................................................................................... 8  
4 Introduction ........................................................................................................................................................................................................ 9  
  4.1 Basic Information ................................................................................................................................................................................................ 10  
  4.2 Safety Considerations .............................................................................................................................................................................. 11  
  4.3 Rationale for the Study .............................................................................................................................................................................. 12  
5 Objectives and Endpoints .............................................................................................................................................................................. 14  
  5.1 Objectives .................................................................................................................................................................................................... 14  
    5.1.1 Primary Objective .................................................................................................................................................................................. 14  
  5.2 Endpoints .................................................................................................................................................................................................... 14  
    5.2.1 Primary Endpoint .................................................................................................................................................................................. 14  
    5.2.2 Additional endpoint ........................................................................................................................................................................... 14  
6 Study Design .................................................................................................................................................................................................... 14  
  6.1 Type of Study .................................................................................................................................................................................................... 14  
  6.2 Rationale for Study Design ...................................................................................................................................................................... 15  
  6.3 Treatment of Patients .................................................................................................................................................................................. 15  
7 Study Population ................................................................................................................................................................................................... 15  
  7.1 Number of Patients to be Studied .......................................................................................................................................................... 15  
  7.2 Inclusion Criteria ...................................................................................................................................................................................... 16  
  7.3 Exclusion Criteria ...................................................................................................................................................................................... 16  
  7.4 Withdrawal Criteria .................................................................................................................................................................................. 16  
  7.5 Rationale for Study Population .............................................................................................................................................................. 16  
8 Study Schedule ..................................................................................................................................................................................................... 16  
9 Methods and Assessments .............................................................................................................................................................................. 17  
  9.1 Visits .................................................................................................................................................................................................................. 17  
    9.2 Visit Procedures ................................................................................................................................................................................................ 17  
      9.2.1 Screening Visit (Visit 1) ....................................................................................................................................................................... 17  
      9.2.2 Annual or Semi-annual Assessment Visits (Visit 2) .......................................................................................................................... 18  
      9.2.3 End of Study Visit (Visit 50) .............................................................................................................................................................. 18  
  9.3 Demography .................................................................................................................................................................................................. 20  
  9.4 History of bleeding episodes ..................................................................................................................................................................... 20  
  9.5 Bleeding Treatment History ...................................................................................................................................................................... 20  
    9.5.1 Definition of Major Surgery ................................................................................................................................................................. 20  
    9.5.2 Definition of Minor Surgery ................................................................................................................................................................. 21  
  9.6 Medical History .................................................................................................................................................................................................. 21  
  9.7 Details on Diagnosis of Haemophilia and Inhibitors .................................................................................................................................................................................. 21
21 Responsibilities ........................................................................................................................................37

22 Reports and Publications........................................................................................................................37
  22.1 Communication and Publication..................................................................................................38
  22.1.1 Authorship .................................................................................................................38
  22.1.2 Publication(s) ...............................................................................................................38
  22.1.3 Site-Specific Publication(s) by Investigator(s) ..................................................................39
  22.2 Investigator Access to Data and Review of Results ..................................................................39

23 Retention of Observational Study documentation ..............................................................................39

24 Indemnity Statement...............................................................................................................................40

25 References ................................................................................................................................................40

Appendix B Agreement on the Final Protocol
Attachment I - Global List of Key Staff and Relevant Departments
Attachment II - Country List of Key Staff and Relevant Departments

List of figures and tables

Table of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–1</td>
<td>Time Course of Inhibitor Formation in Haemophilia A Patients Undergoing Prophylactic or On-demand Treatment</td>
<td>13</td>
</tr>
</tbody>
</table>

Table of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–1</td>
<td>Flow chart</td>
<td>8</td>
</tr>
<tr>
<td>4–1</td>
<td>Time course of inhibitor formation in previously untreated haemophilia A patients with recombinant factor VIII</td>
<td>13</td>
</tr>
<tr>
<td>8–1</td>
<td>Study Schedule</td>
<td>17</td>
</tr>
</tbody>
</table>
1 List of abbreviations

AE            Adverse Event
CCDS          Company Core Data Sheet
CHMP          European Union’s Committee for Medicinal Products for Human Use, previously known as CPMP
CPMP          European Union’s Committee for Proprietary Medicinal Products
CRF           Case Report Form
CRO           Contract Research Organization
CV            Curriculum Vitae
DCF           Data Clarification Form
eCRF          electronic Case Report Form
EMEA          European Medicinal Evaluation Agency
EU            European Union
EU PI         EU Product Information
FVII:C        Coagulation factor seven clotting activity
FVIIa         Activated coagulation factor seven
FVII          Coagulation factor seven
FIX           Coagulation factor nine
FVIII         Coagulation factor eight
FX            Coagulation factor ten
HTC
Haemophilia Treatment Centres

ICMJE
International Committee of Medical Journal Editors

IEC
Independent Ethic Committee

IMO
International Medical Officer

IRB
Institutional Review Board

MESI
Medical Events of Special Interest

MIDF
Monitor Initiated Discrepancy Form

NA
Not Applicable

ND
Not Done

pCRF
paper Case Report Form

PL
Package Leaflet

rFVIIa
activated recombinant human factor VII (NovoSeven®, Novo Nordisk)

RIA
Radio Immune Assay

SAE
Serious Adverse Event

SmPC
Summary of Product Characteristics

STER
Seven Treatment Evaluation Registry

VII25
rFVIIa room temperature stable (at or below 25°C)
2 Summary

Primary Objective:
The aim of this observational study is to monitor prospectively for decreased therapeutic response and the development of neutralising antibodies towards FVII (FVII inhibitors).

Study Design:
Observational prospective study on room temperature stable NovoSeven® (VII25) in patients with haemophilia A or B with inhibitors.

Study Population:
Fifty male patients with haemophilia A or B with inhibitors treated with VII25 will be screened to allow for at least 40 patients to complete the study.

Assessments:
Adverse events, vital signs, bleeding episodes description, and FVII neutralising antibodies.

Treatment:
Commercially available room temperature stable NovoSeven® prescribed by the haemophilia treatment centres and supplied according to local standard practice. Novo Nordisk will not provide study drug under this protocol.
### 3 Flow Chart

#### Table 3–1 Flow chart

<table>
<thead>
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<th>Study Periods</th>
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4 Introduction

A room temperature stable formulation of activated recombinant human coagulation factor VII (rFVIIa) has been developed to provide a rFVIIa product that can be stored and transported at room temperature allowing greater mobility and drug availability for the users of the product. It is provided as a freeze-dried powder and solvent. In EU the trade name is NovoSeven®. The trade name may vary in countries outside EU depending on local regulations. Upon marketing authorisation approval, this room temperature stable formulation will replace the original NovoSeven® products in the marketplace.

The active pharmaceutical ingredient in the new formulation is exactly the same protein as that in the original products. The main differences between the new and the original formulation are the introduction of three new excipients, L-methionine, sucrose, and L-histidine, and a higher concentration of rFVIIa after reconstitution (1.0 mg/ml versus 0.6 mg/ml of the original one). The three additional excipients are currently used in other licensed, intravenously administered pharmaceuticals in doses that result in greater exposure to these excipients than anticipated for normal use of rFVIIa.

Bioequivalence between the original and the new NovoSeven® formulations has been demonstrated in studies in animals and in healthy human subjects.
Consistent with the original use of NovoSeven®, the new product will mainly be used for the treatment of haemophilia A and B patients with inhibitors towards either factor VIII or factor IX. The prevalence of haemophilia A is approximately 1:5,000 males, and for haemophilia B, 1:30,000 males. Approximately 15-30% of haemophilia A patients and 2-4% of haemophilia B patients develop inhibitors. In total, the inhibitor population constitutes about 3500 – 4000 individuals in the developed world.

This study investigates the potential change in immunogenicity of recombinant activated factor VII (rFVIIa) related to change in drug formulation and/or change in storage conditions from 2-8°C (refrigerated) to 0-25°C (room temperature). The room temperature stable formulation of rFVIIa will for simplicity in this document be called VII25. The investigation is conducted during normal clinical use of VII25 in accordance with the approved product labelling (EU Summary of Product Characteristics, or other local product labelling texts). Therefore, the protocol does not specify inclusion criteria (other than diagnosis), exclusion criteria or dose regimens. Rather, the protocol refers to the approved labelling texts in the country of each participating centre.

The study is limited to haemophilia patients with FVIII or FIX inhibitor status requiring treatment with bypassing agents. In order to collect information needed to characterise the patient population, assessments will be performed at entry and end of the study. To calculate VII25 exposures and to assess potential inhibitor formation based on clinical evaluations or optional blood sampling for measurements of a potential immunological response to the treatment (cross-reacting, activity inhibiting anti-FVII antibodies (FVII:C inhibitors)), information will be collected on an annual or semi-annual basis. As treatment is prescribed by the participating Haemophilia Treatment Centres (HTC) and not affected by the study, no study medication is provided by Novo Nordisk.

The current protocol describes a prospective observational study aiming at documenting long term safety of the room temperature stable formulation of NovoSeven® with special attention to possible neutralising antibody development.

The room temperature stable formulation was approved in the EU on 25 April 2008 (Trade name NovoSeven®) and in the US on 9 May 2008 (Trade name NovoSeven® RT).

4.1 Basic Information

Haemophilia A and B are recessive X-linked congenital bleeding disorders, caused by mutations in either the coagulation factor eight (FVIII) gene or the coagulation factor nine (FIX) gene (haemophilia A and B, respectively) on the long arm of the X-chromosome. Patients with haemophilia A and B either lack or have a reduced production of FVIII or FIX, or they produce biochemically defective FVIII or FIX molecules. With a deficiency or absence of these factors, activation of coagulation factor ten (FX) becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis. The haemostatic plug
formed in these patients is therefore fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis and prolonged bleeding episodes. This especially concerns internal bleeding while external bleeding from skin surfaces is almost normal.

Coagulation factor VIIa (FVIIa) is involved in initiating the coagulation cascade. Clinical development of activated recombinant human coagulation factor VII (rFVIIa) began in 1988 for the treatment of haemophilia patients with inhibitors against coagulation FVIII and FIX. In February 1996 rFVIIa was approved in Europe for the treatment of bleeding episodes and for surgical procedures in haemophilia A and B patients with inhibitors and in February 1999 rFVIIa was licensed in Canada and in March 1999 in the US for the treatment of bleeding episodes in haemophilia A and B patients with inhibitors. Today, the original rFVIIa product (NovoSeven®) is a licensed and marketed product in more than 90 countries. The approved indications, which vary from country to country, include the treatment of bleeding episodes and for the prevention of bleeding during surgery or invasive procedures in patients with haemophilia A or B with inhibitors, acquired haemophilia, FVII deficiency and Glanzmann Thrombasthenia. For most of these indications, the recommended initial dose of NovoSeven®, administered by intravenous bolus injection, is 90 µg/kg. In some countries a single dose of 270 µg/kg BW is approved for the treatment of mild to moderate bleeds.

The original NovoSeven® products contain sterile, white lyophilized powder of rFVIIa in single use vials containing 1.2, 2.4, and 4.8 mg/vial, respectively. These products must be stored at 2-8°C. After reconstitution with the appropriate volume of water for injection, each vial contains approximately 0.6 mg rFVIIa/mL. To facilitate faster access, earlier treatment and less dependency on cooling boxes and refrigerators Novo Nordisk has developed a new formulation (VII25) of the drug product, which allows storage at or below 25°C for the whole shelf life period of 24 months.

Furthermore, in order to facilitate the calculation of the dose needed for the individual patient, the drug product presentations of the new formulation comprise three single use vials of 1, 2, and 5 mg of lyophilized rFVIIa/vial, which after reconstitution with the appropriate volume of solvent all contain approximately 1.0 mg rFVIIa/mL. For details see the European Summary of product Characteristics or Package Leaflet. Therapeutic equivalence between the original and the room temperature stable NovoSeven® has been shown in a bioequivalence study in healthy human subjects.

4.2 Safety Considerations

Through more than 10 years of clinical use, NovoSeven® has shown a very low immunogenic potential in humans. So far no confirmed cases of FVII antibodies have been detected in patients with haemophilia A and B, acquired haemophilia or Glanzmann’s Thrombasthenia. Since licensure only five cases of neutralising antibodies against the FVII molecule (cross reacting neutralising antibody) have been reported; all of these in FVII deficient patients. However, any change in the
formulation, the primary packaging materials or the storage conditions of a biological product may be associated with a potential risk of a change in immunogenicity of a therapeutic protein - increase or decrease.

Compared to the original NovoSeven® the VII25 formulation contains three additional excipients: L-methionine, sucrose and L-histidine. These excipients are currently used in licensed i.v. administered pharmaceuticals in doses which result in larger exposure than that anticipated for normal use of NovoSeven®. Bioequivalence between NovoSeven® and VII25 was demonstrated pre-clinically in beagle dogs, and no further demonstration of non-clinical safety is considered relevant.

A clinical study in healthy volunteers has demonstrated bioequivalence in man and no further studies in persons were deemed necessary for registration of the product with the EMEA. Since rFVIIa is an activated clotting factor administered in doses leading to circulating plasma levels considerably higher than the normal plasma-level of FVIIa, it may potentially increase the risk of thrombosis and specific attention has been paid to the occurrence of thromboembolic events in rFVIIa treated patients. However, as indicated above, NovoSeven® has been in extensive clinical use since 1996 and given in several studies to healthy volunteers in higher doses and VII25 has been administered in clinically relevant doses in healthy volunteers without any safety issues or concern. Thus, it is concluded that potential risks of administering VII25 in patients with haemophilia are minimal.

4.3 Rationale for the Study

The purpose of this observational study is to investigate a potential change in immunogenicity related to a change in formulation and storage conditions during normal clinical use of NovoSeven® (VII25) in patients with haemophilia A or B with inhibitors, the largest of the patient populations for which NovoSeven® is licensed.

As no documented cases of inhibitor development against rFVIIa in haemophilia patients exist at present we have no direct evidence with regard to risk factors upon which to base the study design. Using the data available for inhibitor development in Haemophilia A and B exposed to FVIII or FIX products it has been decided that the patients are to be treated with VII25 for at least 25 exposure days.

The rationale for the 25 exposure days is based on the experiences with the time course of inhibitor formation in patients with haemophilia A treated with FVIII products. The median exposure days before inhibitor formation is 9 to 17 days, Table 4–1 and at 25 days the cumulative incidence has levelled out and only a few additional inhibitor cases develop subsequently, Figure 4–1.
Table 4–1  Time course of inhibitor formation in previously untreated haemophilia A patients with recombinant factor VIII

<table>
<thead>
<tr>
<th>Studies</th>
<th>Product</th>
<th>Median exposure days before inhibitor development (range)</th>
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<tr>
<td>Rothschild C et al. TH 1998; 80: 779-83</td>
<td>Recombinate</td>
<td>17 (3 – 69)</td>
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<td>Lusher JM et al. JTH 2004; 2: 574-83</td>
<td>Kogenate</td>
<td>9 (3 – 24)</td>
</tr>
</tbody>
</table>

Figure 4–1  Time Course of Inhibitor Formation in Haemophilia A Patients Undergoing Prophylactic or On-demand Treatment


Studies of inhibitor development in patients with haemophilia A are generally conducted in patients in prophylactic treatment and patients are normally treated for at least 50 exposure days. Our study will mainly be conducted in patients who utilize on-demand treatment for acute bleeds. The time to reach 25 exposure days in these patients is impossible to predict and may be rather long. As there may be a tendency that prophylaxis results in a lower incidence of inhibitors than on-demand treatment, Figure 4–1, Novo Nordisk considers 25 exposure days as described in section 9.13 for an adequate exposure to evaluate a potential change in immunogenicity caused by the change in formulation and/or storage conditions. Calculations based on actual FVII inhibitor frequency are not possible as these have never been detected in the haemophilia population.
5 Objectives and Endpoints

5.1 Objectives

5.1.1 Primary Objective

The aim of this observational study is to monitor prospectively for decreased therapeutic response and the development of neutralising antibodies towards FVII (FVII inhibitors).

5.2 Endpoints

5.2.1 Primary Endpoint

Structured reporting of cases of reduced therapeutic response and FVII neutralising antibodies in patients with haemophilia A and B with inhibitors using the room temperature stable formulation of NovoSeven® (VII25).

5.2.2 Additional endpoint

Adverse events reported as potentially related to NovoSeven®.

6 Study Design

6.1 Type of Study

This is a prospective, observational, single-arm, multi-centre, multinational study on detection of antibodies to FVII in relations to treatment with VII25 in haemophilia A (Factor VIII) and haemophilia B (Factor IX) patients with inhibitors. There will be no dispensing of any study medication associated with participation in this study. All direction for medication usage is solely at the discretion of the physician in accordance with their usual care.

Baseline information regarding patient demographics, haemophilia treatment history, medical history and bleed history will be collected from the investigational site at the time of patient enrolment.

Patients are expected to remain in the study for a period of up to two years and will be offered testing for FVII neutralising antibodies at entry into the study (baseline), at the end of the study period and when judged by the treating physician to be clinically indicated. The investigator is strongly encouraged to perform blood testing for inhibitory antibodies in the presence of clinically reduced therapeutic response and once to twice annually if blood sampling is performed as routine practice during the voluntary assessment visit offered by Novo Nordisk. At least 40 patients will be observed in this study. The study may be terminated when at least 40 patients have reached 25 exposure days.
The study assesses neutralising antibody development in haemophilia inhibitor patients treated with VII25, who have been screened for inclusion and have signed informed consent for participation in the observational study. Any patient evaluated as eligible for the study at the pre-study evaluation will be offered to participate in the study.

6.2 Rationale for Study Design

The rationale for choosing a multi-centre design is to ensure sufficient screening pool of patients for the study. The treatment regimens will be in accordance with the approved labelling in the patient's home country. The powering of the study with a total of 40 patients treated for 25 exposure days allows for an upper 95% confidence limit of 7.22% for the incidence of neutralising antibody formation provided none of the patients are tested positive for neutralising antibodies. Lack of efficacy could be indicative of neutralising antibodies. It must be remembered that lack of efficacy has numerous other clinical reasons of which antibody development is the least likely. As no neutralising antibody has been detected in the study population during the ten years NovoSeven® has been in commercial use and as the new formulation contains exactly the same rFVIIa molecule, this is evaluated to be the most likely outcome. Patients with haemophilia A and B have been chosen as they are in quantitative terms those who are most likely to be exposed and benefit from treatment with VII25.

6.3 Treatment of Patients

Each patient will administer VII25 (Commercially available room temperature stable NovoSeven®) in dosages prescribed by his Haemophilia Treatment Centre according to the product labelling text approved in his country (Summary of Product Characteristics (EU) or corresponding local prescribing information).

7 Study Population

7.1 Number of Patients to be Studied

Countries planned to participate: Countries where VII25 is licensed, e.g. European countries, Argentina and Iran.

Planned number of patients to be screened (i.e. documented informed consent): 50

Planned number of patients to be included in the study: 50

Planned number of patients to complete the study: 40

Anticipated number of study sites: 10-20

Anticipated number of patients to be included in the study at each study site: 2-4
7.2 **Inclusion Criteria**

1. Male patients with diagnosis of congenital haemophilia A or B with inhibitors to FVIII or FIX treated with commercially available room temperature stable NovoSeven® (VII25); only patients expected to receive therapy for at least 25 exposure days should be enrolled. Patients initiating immune tolerance induction treatment can stay in the study provided breakthrough bleeds are treated with VII25.
2. Able and willing to provide signed informed consent (or proxy/caregiver consent, if applicable), as required by local ethics committee, governmental or regulatory authorities.
3. Adequate venous access at the Screening Visit.

7.3 **Exclusion Criteria**

No exclusion criteria beyond the contraindications of the relevant approved product information text (European SmPC and PL).²

7.4 **Withdrawal Criteria**

If the patient is permanently discontinued on VII25, for any other reason than development of neutralising antibodies to FVII, the patient must be withdrawn from the study. If the discontinuation of VII25 is related to formation of neutralising antibodies to FVII the patient should remain in the study until his antibody titre has reached levels below detection level.

The patient may withdraw their consent at will at any time.

The patient may be withdrawn from the study at the discretion of the Investigator or the Sponsor due to a safety concern or if judged non-compliant with study procedures.

7.5 **Rationale for Study Population**

The study population of haemophilia A and B patients with inhibitors to factor VIII or IX routinely treated with bypassing therapy is selected as this is the group of patients most frequently exposed to the drug and benefiting the most from the treatment. Haemophilia patients with inhibitors have no licensed indication for prophylactic treatment hence these patients cannot be selected for the study. Patients with FVII deficiency are studied in the STER³ registry. Patients with acquired haemophilia are generally only treated once in a life time and immunogenicity is not considered a serious risk in these patients. Patients with Glanzmann's thrombasthenia are very rare and exposed less frequently than patients with haemophilia. Furthermore, the use of NovoSeven® for the treatment of patients with Glanzmann's thrombasthenia is not approved in all countries.

8 **Study Schedule**

Timelines may be adjusted during the course of this observational study.
Table 8–1 Study Schedule

<table>
<thead>
<tr>
<th>Milestone*</th>
<th>Timeline</th>
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<td>Site initiation begins</td>
<td>Q3 2010</td>
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<tr>
<td>First patient enrolled</td>
<td>Q3 2010</td>
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<tr>
<td>Last patient enrolled</td>
<td>Q3 2012</td>
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<td>Last patient completed (Assumes 2 years for minimum # bleeds)</td>
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<td>Second interim data analysis</td>
<td>Q3 2013</td>
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<tr>
<td>Final study report</td>
<td>Q3 2015</td>
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</table>

*All milestones are estimated and predicated upon reaching the first milestone.

9 Methods and Assessments

9.1 Visits

It is the intention not to interfere with the routine treatment of the individual patients. Therefore, the assessments are limited to:

1. examinations and collection of information needed to characterise the patient population at initiation and at the end of the study,
2. optional collection of blood samples for analysis of FVII inhibitor development. Procedures for the scheduled visits are described in the subsections below.

9.2 Visit Procedures

9.2.1 Screening Visit (Visit 1)

Signed informed consent must be obtained before any data recording (including optional blood sampling) is performed for the purpose of this observational study.

The following will be performed at the Screening Visit, after having obtained informed consent:

- Check of inclusion and exclusion criteria (Please refer to Section 7.2 and 7.3)
- AE assessment (Please refer to Section 12)
- Demography (Please refer to Section 9.3)
- History of bleeding episodes (Please refer to Section 9.4)
9.2.2 Annual or Semi-annual Assessment Visits (Visit 2)

Assessment for FVII antibodies may be performed annually or semi-annually after the Screening Visit at the discretion of the treating physician and with consent from patient until 25 exposure days is completed.

When assessing for FVII antibodies the following will be performed:

- Assessment of VII25 exposure
  - Calculation of exposure days (Please refer to Section 9.13)
  - If 25 exposure days have been reached schedule End of Study Visit (Please refer to Section 9.2.3)
- Assessment of treatment of bleeding episodes since last visit
  - Review of each bleeding episode since last visit (Please refer to Section 9.9)
  - Assessment of ineffective treatment episodes, if any
  - Body weight (Please refer to Section 9.8)
- Haemostatic treatment not related to bleeding episodes (Please refer to Section 9.12)
- If judged warranted by the treating physician sampling for analysis of cross reaction neutralising antibodies (Please refer to Section 9.10.1.1)
- AE assessment (Please refer to Section 12)
- Concomitant illness assessment (Please refer to Section 11)
- Concomitant medication assessment (Please refer to Section 11)
- Diary evaluation
- Assessments for withdrawal criteria (Please refer to Section 7.4)

9.2.3 End of Study Visit (Visit 50)

- The End of Study visit will be performed 4 weeks after the patient has had 25 exposure days or is withdrawn from the study.
This visit may either be performed as an on-site visit or performed remotely. Whenever possible an on-site visit should be done. However, in cases where an on-site patient visit might not be planned "as per the standard of care" a remote visit may be considered.

**On-Site End of Study Visit**

The following will be performed at the on-site end of study visit:

- AE assessment (Please refer to Section 12)
- Body weight (Please refer to Section 9.8) Bleeding episodes description (Please refer to Section 9.9)
- Vital signs (Please refer to Section 9.10.2)
- Optional sampling for cross reaction neutralising antibodies (Please refer to Section 9.10.1.1)
- Diary evaluation
- Exposure days (Please refer to Section 9.13)
- Dose regimen (Please refer to Section 9.11)
- Concomitant illness assessment (Please refer to Section 11)
- Concomitant medication assessment (Please refer to Section 11)
- Date and reason for early discontinuation (only relevant for patients discontinuing before 25 exposure days have been reached).

**Remote End of Study Visit:**

- In cases where a patient visit is not planned "as per the standard of care" and the patient is not able to return to the study site for the End of Study Visit, a remote End of Study Visit may be done to ensure collection of all necessary information. The remote End of Study Visit will be done by telephone interview whereby the treating physician calls the patient to retrieve all necessary information. This interview will be documented on worksheets which will serve as source document. Upon completion of the interview all information will be entered in the eCRF.

The following will be performed at the remote end of study visit:

- AE assessment (Please refer to Section 12)
- Bleeding episodes description (Please refer to Section 9.9)
- Diary evaluation (to evaluate diary data the treating physician will request all necessary information during the telephone interview)
- Exposure days (Please refer to Section 9.13)
- Dose regimen (Please refer to Section 9.11)
- Concomitant illness assessment (Please refer to Section 11)
- Concomitant medication assessment (Please refer to Section 11)
• Date and reason for early discontinuation (only relevant for patients discontinuing before 25 exposure days have been reached).

9.3 Demography

The following demography parameters will be recorded at the Screening Visit.

• Date of birth
• Ethnic background

9.4 History of bleeding episodes

Bleeding frequency as reported by the patient

9.5 Bleeding Treatment History

• On-demand regimen as reported by the patient
  • Average number of bleeding episodes per month within the last 12 months
  • Bypassing product (name, and formulation if available)
  • Recombinant or plasma FVIII product
  • Recombinant or plasma FIX product
  • Prophylaxis (if yes: time period, drug name and dose regimen)
  • Immune tolerance induction (if yes, ongoing or finalized)
• Surgeries within the last 5 years
  • Date of surgery
  • Type of surgery (minor/major)
  • Bypassing product (name, and formulation if available)

9.5.1 Definition of Major Surgery

Major surgery is any invasive operative procedure where any one or more of the following occur.

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

These procedures may be performed using general anaesthesia, spinal anaesthesia, epidural anaesthesia, conscious sedation or with a combination of these modalities.
9.5.2 Definition of Minor Surgery

Minor surgery is any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated. Examples of minor surgery include vascular cutdown for catheter/fistula placement, implanting pumps or ports in subcutaneous tissue, biopsies or placement of probes, leads, or catheters requiring the entry into a body cavity only through a needle/guidewire.

Dental surgery will be classified as minor or major based on above definitions.

9.6 Medical History

Details on medical history and concomitant illnesses will be recorded at the Screening Visit by a medical interview and review of relevant medical records.

- The following will be documented:
  - Diagnosis of haemophilia A or haemophilia B
  - Details of inhibitor history (Please refer to Section 9.7)
  - The diagnosis of intercurrent acquired coagulation disorders, other than haemophilia A or B;
  - Use of Concomitant Medication;
  - Chronic infectious diseases and recent vaccinations.

During the study period, changes in Concomitant Illnesses will be recorded until end of study visit after 25 exposure days.

9.7 Details on Diagnosis of Haemophilia and Inhibitors

A positive inhibitor test for FVIII or FIX is defined as $\geq 0.6$ Bethesda Unit (BU)/mL or the cut off value relevant for the assay used at time of assessment.

- Diagnosis of haemophilia A or B and date of diagnosis
  - Current inhibitor value
  - Date of first diagnosis of inhibitor
  - Highest inhibitor titre recorded (‘historical peak titre’)
  - Underlying gene defect (if known)

9.8 Body Measurements

Height (cm) without shoes will be measured at the Screening Visit

Body weight (kg) will be recorded with standardised scale (patient in light clothing and without shoes) at each visit.
9.9 Bleeding Episodes Description

All bleeding episodes will be recorded in a diary and transferred to the CRF at the regular assessment visit by the Investigator:

The following information will be collected for each bleeding episode:
- Date and time of onset of bleeding
- Approximate time from detection of bleed to first VII25 administration
- Cause of bleeding (spontaneous or traumatic)
- Site of bleeding
- Date and time of bleeding resolution
- Haemostatic therapy used
  - Product name
  - Dose and regimen
  - Treatment outcome
- Concomitant illness in relation to bleeding episodes
- Concomitant medication in relation to bleeding episodes, e.g. antifibrinolytics

9.10 Assessments for Safety

All adverse events, either observed by the investigator or reported by the patient must be recorded and evaluated by the investigator.

9.10.1 Central Laboratory Tests

A central laboratory will analyse and report laboratory tests performed in this study-related to FVII cross reaction neutralising antibody assessment. Laboratory data from the Central Laboratory will be reported to Novo Nordisk electronically. Laboratory data will be reported to Novo Nordisk in a manner that anonymity of patients will be maintained.

The quality control of the Central Laboratory test results will be performed according to the regulations and specifications set by the authorities at the location of the Central Laboratory used for this study.

9.10.1.1 FVII Antibodies

When judged necessary by the treating physician and with consent from patient, blood samples will be drawn by venipuncture prior to any planned FVII injection for neutralising antibody (inhibitor) detection.

Samples for neutralising antibodies may be taken:
- Prior to entry into the study
• At annual or semi-annual visits
• Upon 25 exposures
• In case of reduced or ineffective response to treatment. Investigators are strongly encouraged to perform blood testing for inhibitory antibodies in the presence of clinically reduced therapeutic response or when less than expected.

The antibody assessment is a stepwise process involving three individual tests:

1. All plasma samples are screened for rFVIIa binding antibodies by a radio immunochemistry (RIA) screening assay. If negative, no further testing is required.
2. Positive plasma samples detected in the screening assay will be confirmed for anti-rFVIIa antibodies in a confirmatory immunochemistry (RIA) assay.
3. Plasma samples with confirmed antibodies towards rFVIIa will be tested in an FVII: C assay for cross-reacting neutralising effect towards endogenous FVII and FVIIa.

Antibody Screening

A blood sample for screening of antibodies against rFVIIa could be taken at entry into the study, at termination of the study and as deemed clinically relevant by the treating physician especially in relation to detection of: Therapeutic response decreased. Antibodies are detected in a radio immunoassay (RIA), where the antibody binding to soluble rFVIIa 125I-tracer is detected using protein G sepharose beads and anti-IgG+IgM+IgA as secondary bridging antibodies.

Positive reactions are confirmed by inhibition with excess of unlabelled rFVIIa. If antibodies towards rFVIIa are confirmed the sample will be analysed for cross-reacting endogenous FVII neutralising effect.

Neutralising Antibody Assay

The neutralising antibody assay is a FVII: C clot activity assay where the presence of endogenous FVII and FVIIa neutralising antibodies is identified through inhibition of coagulation. The patient sample is mixed with a normal plasma pool and the time to clot is registered as a measure of endogenous FVII and FVIIa activity. The presence of neutralising antibodies towards endogenous FVII and FVIIa will prolong the clotting time.

For storage, handling, dispatch, and disposition of samples analysed for FVII cross reaction neutralising antibodies at the Central Laboratory selected by Novo Nordisk, further detailed guidance can be found in the Laboratory Manual.
Positive Neutralising Antibody Assay

If a patient has a positive response for neutralising antibodies to FVIIa it is highly recommended that a confirmatory sample is analysed.

If the patient is permanently discontinued on VII25 the patient must be withdrawn from the study as described in section 7.4. If the patient is not permanently discontinued on VII25 he is allowed to stay in the study.

The positive neutralising antibody test must be reported as a MESI as described in section 12.2.2.

9.10.2 Vital Signs

- Standard safety-related vital signs will be recorded at the Screening visit and at the End of Study visit.
- Body temperature (assessed by measuring ear temp.)
- Pulse: supine after 3 min rest
- Blood pressure: supine after 3 min rest
- Respiratory rate /min
- Blood pressure and pulse rate will be measured using an automatic device; after the patient has rested comfortably for 3 min. Measurements will be reported in the CRF.

9.10.3 Other Assessments

For each FVII antibodies assessment a volume of approximately 3 mL blood will be taken.

9.11 Patient Compliance

All doses will be administered in accordance with the package inserts. All information regarding administration of medication will be captured in a patient diary and transferred to the CRF by the Investigator.

9.12 Haemostatic treatment not related to bleeding episodes

All haemostatic treatment not related to bleeding episodes that is dispensed outside the hospital/clinic will be recorded in a patient diary. The diary will be discussed and transferred to the CRF at the assessment visits by the Investigator.

Haemostatic treatment given at the hospital/clinic will be recorded in the patient's medical records following standard practice at the hospital/clinic.

The following information will be collected for each haemostatic treatment not related to a bleeding episode:
• Date medication given
• Medication name
• Dose/regimen
• Reason

9.13 Exposure Days

Exposure days are defined based on an exposure to VII25. If two or more doses of VII25 are administered on the same day, this is only registered as one exposure day. If treatment continues beyond 24 hours, each initiated 24 hours period is considered an exposure day. The number of exposure days to VII25 will be captured in a patient diary and transferred to the CRF at the assessment visit by the Investigator.

10 Study Supplies

10.1 Treatment

Commercially available room temperature stable NovoSeven® (VII25) used according to the approved package insert (SmPC).

If additional presentations become commercially available during the study Novo Nordisk will ensure that relevant local authorities are informed as required. The medication will not be supplied by Novo Nordisk.

11 Concomitant Illnesses and Medication

Definitions:

Concomitant Illness: any illness that is present at the start of the study (i.e. at the first visit).

Concomitant Medication: any medication other than VII25 that is taken during the study, including reported at the screening visit.

Details of all Concomitant Illnesses and Medication must be recorded at study entry (i.e. at the first visit). Any changes in Concomitant Medication must be recorded at each visit. If the change influences the patient’s eligibility to continue in the study, the Sponsor must be informed.

The information collected for each Concomitant Medication includes, at a minimum, start date, stop date or continuing and indication.

Bleedings related to Haemophilia A and Haemophilia B must be reported as Bleeding assessments (Please refer to Section 9.9) and related haemostatic treatment as Concomitant Medication.

Other medical diseases or emergencies can be treated according to local hospital practices.
12 Adverse Events

12.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should not be recorded as AEs:

Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first administration of VII25 after the patient has signed the informed consent.

Pre-existing conditions found as a result of screening procedures. These should be recorded as Medical History/Concomitant Illness.

An AE can also be a clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity which requires active management (i.e. change of dose, discontinuation of VII25, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE):

A Serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening* experience
- In-patient hospitalisation* or prolongation of existing hospitalisation
- A persistent or significant disability/incapacity*
- A congenital anomaly/birth defect
- Important medical events * that may not result in death, be life-threatening*, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
The term "life-threatening" in the definition of SAE refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

The term "hospitalisation" describes a period of at least 24 hours. Over-night stay for observation, treatment at emergency room or treatment on an out-patient-basis does not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious.

Hospitalisations for administrative, study-related and social purposes do not constitute hospitalisations as defined by the seriousness criteria for SAEs and should therefore not be reported as such. Likewise, hospital admissions for surgical procedures planned prior to study inclusion are not considered AEs.

The term "disability/incapacity" means that following the event the patient or clinical investigation patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life.

The term "important medical events" means events which may jeopardise the patient or require intervention to prevent a seriousness criterion. It can be AEs which suggest a significant hazard or puts the patient or clinical investigation patient at risk, such as drug-interactions, contra-indications or precautions, occurrence of malignancies or development of drug dependency or drug abuse.

Non-serious AE:
A non-serious AE is any AE which does not fulfil the definition of a serious AE.

Severity Assessment Definitions:
- **Mild** - No or transient symptoms, no interference with the patient's daily activities.
- **Moderate** - Marked symptoms, moderate interference with the patient's daily activities.
- **Severe** - Considerable interference with the patient's daily activities, unacceptable.

Relationship to VII25 Assessment Definitions:
- Probable: good reasons and sufficient documentation to assume a causal relationship
- Possible: a causal relationship is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to an aetiology other than VII25.
Outcome Categories and Definitions:

- **Recovered** - Fully recovered, or by medical or surgical treatment the condition has returned to the level observed prior to participation in the observational study after the patient signed the informed consent.
- **Recovering** - The condition is improving and the patient is expected to recover from the event. This term should only be used when the patient has completed the study.
- **Recovered with sequelae** - As a result of the AE the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE.
- **Not recovered**.
- **Fatal**.
- **Unknown** - This term should only be used in cases where the patient is lost to follow-up.

### 12.2 Collection, Recording, and Reporting of AEs

All events meeting the definition of an AE must be collected and reported. At each contact with the study site, the patient must be asked about AEs. All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated.

SAEs will be reported from inclusion to end of study. Non-serious AE will be reported in relation to bleeds/VII25 administrations from administration until 7 days post last administration of VII25. SAEs, including "therapeutic response decreased/lack of efficacy", must be reported to the treating physician immediately. Other AEs are reported by the patient to the treating physician. At each visit the physician or nurse will interview the patient about AEs.

Sponsor's assessment of expectedness is done using the at all times current company core data sheet for room temperature stable NovoSeven® as the reference document:

The Investigator should record the diagnosis, if available. If no diagnosis is available the Investigator should record each sign and symptom as individual AEs.

The Investigator should record signs and symptoms as individual AEs in addition to reporting the diagnosis (when known) and which signs/symptoms are covered by the diagnosis (linking).

All AEs must be recorded by the Investigator on the standard AE form. If more than one sign or symptom is to be reported, use a separate AE form for each sign and symptom. For serious AEs, the Safety Information Form must also be completed.

The Investigator must report initial information on all serious AEs to Novo Nordisk within 24 hours of obtaining knowledge about the event.
The Investigator must complete and forward electronically/fax/courier copies of the AE form and the safety information form to Novo Nordisk within 5 calendar days of obtaining knowledge about the serious AE.

For non-serious AEs all initial information must be reported to Novo Nordisk within 14 days of the site learning of the event.

AE data must as a minimum be transferred to Novo Nordisk headquarters every six months (or be available for review) with a final data transfer within six months of last patient last visit.

The Sponsor must inform the regulatory authorities and IECs/IRBs in accordance with the local requirements on observational studies in force, if applicable.

The sponsor will notify the Investigator of VII25 related suspected unexpected serious adverse reactions in accordance with the local requirements on observational studies. In addition, the Investigator will be informed of any study-related procedure SAE which may warrant a change of any study procedure.

Investigators will be notified of study-related SAEs in accordance with the local requirements in force.

The Monitor must be informed accordingly.

If during this non-interventional study, a Novo Nordisk representative is informed of any other safety information (i.e. safety information which is not collected as part the systematic collection, as described in this protocol) and related to a Novo Nordisk product, he/she should report this as solicited safety information within 24 hours to the local department responsible for drug safety.

Other safety information during the use of a Novo Nordisk product, i.e. safety information which is not collected as part the systematic collection, includes drug abuse or misuse and technical complaints.

Voluntary reporting of other safety information by the physician should follow the same reporting process flow as for systematic collection. The local department responsible for drug safety will handle the voluntary reports and may request follow-up information as per their statutory requirements.

12.2.1 Bleeding Episode Evaluated as Part of the Underlying Disease and not Related to VII25

Disease related medical events are AEs which do not require reporting as AEs as defined above in section 12.2. All fatal bleeding episodes must be reported as a SAE. All other bleeding episodes evaluated by the Investigator as part of the underlying disease should be reported in the CRF and
not as standard AEs on the AE form and safety information form unless evaluated as related to VII25

12.2.2 Medical Events of Special Interest

The following are defined as Medical Events of Special Interests (MESIs):

- Events such as medication errors (e.g. wrong drug administration or wrong route of administration) and suspected transmission of an infectious agent via VII25.
- Thromboembolic events. This applies to clinical signs, laboratory indications and investigations indicating arterial or venous thrombosis.
- Inhibitor formation, such as inhibitory antibodies against FVII. If an investigator obtains any indication of inhibitor formation by clinical signs or laboratory results.
- Lack of efficacy.

MESIs must always be reported to the department responsible for product safety in the local Novo Nordisk Affiliate on AE form and Safety Information Form irrespectively of seriousness. For non-serious MESIs the AE form and the Safety Information Form must be completed and forwarded to Novo Nordisk Affiliate safety department within 14 calendar days.

12.3 Follow-up of AEs

During and following a patient's participation in a clinical study, the Investigator/institution should ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values related to the study. The Investigator/institution should inform the patient when medical care is needed for AEs of which the Investigator becomes aware.

The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

All non-serious AEs classified as severe or possibly/probably related to the VII25 must be followed until the patient has recovered and all queries have been resolved. However, cases of chronic conditions can be closed with an outcome of "recovering" or "not recovered". If patients die from another event, these cases can be closed with an outcome of "recovering" or "not recovered".

All other non-serious AEs must be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. If patients die from another event, these cases can be closed with an outcome of "recovering" or "not recovered".
The Investigator must ensure that the worst case severity and seriousness is kept consistent through the series of AE form and related AE follow-up form(s).

For sites using electronic Case Report Forms (eCRFs) the investigator must forward follow-up information on non-serious AEs by updating the AE form in the EDC application. For sites using paper Case Report Forms (pCRFs) follow-up information on non-serious AEs must be entered on a new AE form in the pCRF clearly stating the relation to the initial AE.

Queries or follow-up requests from Novo Nordisk should be responded to within 14 calendar days, unless otherwise specified. The Investigator must forward follow-up information on serious AEs to Novo Nordisk within 5 calendar days of obtaining the follow-up information.

All serious AEs must be followed until the outcome of the event is recovered, recovered with sequelae or fatal and until all queries have been resolved. For cases of chronic conditions and cancer or if the patient dies from another event follow-up until the outcome categories are "recovered", "recovered with sequelae" or "fatal" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered".

The Investigator must forward follow-up information on serious AEs using the AE form and/or the safety information form.

12.4 Reports of Pregnancy

As only males are included in the observational study only information of pregnancy in patient's partner should be reported to Novo Nordisk. Patients should be instructed to notify the site immediately if their partner becomes pregnant while participating in this observational study.

The Investigator must report any pregnancy reported during the study to Novo Nordisk except for pregnancies occurring in the screening period. Study subjects will give consent on enrolment that the Investigator will report any pregnancy during the study to Novo Nordisk and that the subject will be asked to provide information about the pregnancy, delivery and the health of the infant until age one month. The investigator must obtain written informed consent from the study participant's partner prior to collection of any pregnancy related information. The Investigator must report information on pregnancy and follow-up within 14 calendar days of obtaining the information using the pregnancy form part A and the pregnancy form part B respectively.

In case of an AE (with a causal relationship evaluated as possible or probable by the Investigator) in the foetus, new born infant(s) or infant(s)/toddler(s) of a study participant's partner, who is potentially exposed to the VII25 via the study patient, the pregnancy and the AE should be reported on the same forms as for a patient in the study.
12.5 Precautions/Over-dosage

Please refer to package leaflet (PL).²

12.6 Safety committee

The surveillance of the laboratory safety data will be performed by the International Medical Officer (IMO) at Novo Nordisk. The IMO will present result of on-going laboratory surveillance at each Safety Committee meeting.

12.6.1 Internal Novo Nordisk safety committee

Novo Nordisk will constitute an internal Safety Committee.

13 Case Report Forms

Novo Nordisk will provide a system for Electronic Data Capture in the form of eCRFs. Additionally, in countries where Electronic Data Capture is not possible pCRFs will be made available for use.

13.1 Rules for completing CRFs

For eCRFs:
Ensure that all questions are answered and that no empty data blocks exist. If a test/assessment has not been done and will not be available, indicate this according to the data entry instructions. Further guidance can be obtained from the instruction in the CRF.

The investigator staff must ensure that all information derived from source documentation is consistent with the source information. By signing the affirmation statement, the Investigator confirms that the information is complete and correct.

For pCRFs:
Print legibly using a ballpoint pen. Ensure that all questions are answered and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks.

If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the respective answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the respective answer field. Further guidance can be obtained from the instruction in the CRF.

By signing the affirmation statement, the Investigator confirms that the information is complete and correct.
13.2 Corrections to CRFs

For eCRFs:
If corrections are made by the Investigator's authorised staff after the date of the Investigator's signature on the affirmation statement, the statement must be signed and dated again by the Investigator.

If the affirmation statement for the patient has not been signed, corrections must be approved by the Investigator or her/his authorised staff. If the affirmation statement for the patient has been signed, only the Investigator can approve the correction.

For pCRFs:
Corrections to the data on the CRFs must only be made by drawing a straight line through the incorrect data and by writing the correct value next to data that has been crossed out. Each correction must contain initials, date and explanation (if necessary) by the Investigator or the Investigator's authorised staff.

If corrections are made by the Investigator's authorised staff after the date of the Investigator's signature on the affirmation statement, the statement must be signed and dated again by the Investigator.

Corrections necessary after the CRFs have been removed from the Investigator's site must be documented on a data clarification form (DCF). Such corrections must be approved by the Investigator or her/his authorised staff.

13.3 CRF Flow

CRFs will be provided by Novo Nordisk as a web-based solution, if this is not feasible a paper based CRF will be provided.

13.4 Analysis Results

Laboratory reports from Central laboratory will be provided the Investigator for information only.

14 Data Management

Data management is the responsibility of Data Management, Novo Nordisk Headquarters. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or external Contract Research Organization (CRO).

The patient and the biological material obtained from the patient will be identified by a patient number, study site, and study ID number. Appropriate measures such as encryption or deletion will
be enforced to protect the identity of human patients in all presentations and publications as required by local/regional/national requirements.

Laboratory data will be transferred electronically from the Central Laboratory performing clinical analyses. The electronic laboratory data will be considered source data. In cases where laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer.

At least one cleaning milestone will take place after completion of 20 patients.

15 Monitoring Procedures

During the course of the study, Novo Nordisk or contracted CRO personnel will monitor the study sites at random intervals. The purpose of these visits is to ensure that the CRFs are completed correctly, the protocol adhered to and to collect completed CRFs.

16 Evaluability of Patients for Analysis

All patients will be included in the safety analysis.

17 Statistical Considerations

Novo Nordisk will be responsible for all statistical analyses.

17.1 Sample Size Calculation

In the current study we plan to have a sample size of 40 patients. If no clinically relevant antibodies are reported the upper 95% confidence limit for the true inhibitor rate will be 7.2%. Due to the small target population this confidence interval is deemed reasonable.

17.2 Statistical Methods

No statistical testing will be performed. All reporting will be descriptive only. A Statistical Analysis Plan will be finalised before database release.

17.2.1 Demographics

All baseline demography including history of bleeding episodes, medical history and concomitant medication will be summarised and listed.

17.2.2 Safety Analysis

The primary endpoint of neutralising antibodies will be listed and a 1-sided 95% confidence interval for the upper limit of the true inhibitor rate will be provided. A structured report will be provided for cases of decreased therapeutic response and cases of positive neutralising antibodies, whereby a
patient profile will be fully described from patient medical charts as documented by the treating physician.

All safety endpoints will be summarised and listed. This covers presence of neutralising FVII antibodies in collected blood samples, adverse events, serious adverse events, bleeding episode description, laboratory assessments, body weight, physical examination, FVIII or FIX antibody titer, and vital signs.

18 Ethics

The study will be conducted in accordance with Good Pharmacoepidimiology Practices (GPP)\(^5\) and applicable regulatory requirements and in accordance with the Declaration of Helsinki\(^6\).

When a patient's participation in the study ends, the patient will consult with his Investigator to decide on the best available treatment.

18.1 Informed Consent Form for Study Patients

In obtaining and documenting informed consent, the Investigator must comply with any local country requirements and the requirements in the Declaration of Helsinki\(^6\).

Prior to enrolment of patients, the Investigator must give the patient (and/or parents or the patient's legally acceptable representative) oral and written information about the observational study in a form that the patient can read and understand. This includes the use of impartial witness where required.

A voluntary, signed, and personally dated Informed Consent Form will be obtained from the patient prior to any observational study-related activity.

If the patient is under age, the investigator and the parents/patient's legally acceptable representative will evaluate if the patient is at a level of maturity whereby the patient can sign the informed consent. National regulation on obtaining informed consent from patients under age must be observed. This signature does not substitute the signature of the parent(s) or the patient's legally acceptable representative.

The responsibility for obtaining informed consent must remain with that of a medically qualified person and cannot be delegated to a non-medically qualified person. The written informed consent must be signed and personally dated, by the person who obtained the informed consent.

If information becomes available that may be relevant to the patient's willingness to continue participating in the study, the Investigator must inform the patient in a timely manner, and a revised written informed consent must be obtained.
The Investigator should keep signed and dated Informed Consent Forms together with signed and dated print-outs of all data collected in the study in the patient medical file.

18.2 Data handling

If the patient withdraws the previously given Informed Consent the patient's data will be handled as follows:

- Data collected will be used as part of the per protocol/intention to treat population.
- Safety events will be reported to the department responsible for global product safety, Novo Nordisk/regulatory authorities.

If data is used, it will always be in accordance with local law and IRB/IEC procedures.

18.3 Institutional Review Boards/Independent Ethics Committee

Prior to commencement of the study, the protocol, any amendments, patient information/Informed Consent Form, any other written information to be provided to the patient, patient recruitment procedures, if any, information about payments and compensation available to patients if not mentioned in the patient information, the Investigator's current CV and/or other documentation evidencing qualifications, and other documents as required by the local institutional review board (IRB)/independent ethics committee (IEC) should be submitted. The submission letter should clearly identify (by study identification number, including version, title and/or date of the document) which documents have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC prior to commencement of the study.

During the study, the Investigator must promptly in accordance with local requirements report the following to the IRB/IEC: unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the study status and other documents as required by the local IRB/IEC.

Substantial amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate hazards to the patients.

The Investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records should be filed in the Investigator's study file and copies must be sent to Novo Nordisk.
19 Premature Termination of the Study

The Sponsor, Investigator or a pertinent regulatory authority may decide to stop the study or part of the study at any time but agreement on procedures to be followed must be obtained. The study is an activity of a Risk Management Plan approved by the EMA/CHMP and can only be prematurely terminated if accepted by these agencies.

If a study is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Investigator and/or Sponsor should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

20 Critical Documents

Before the Investigator starts the study (i.e. obtains Informed Consent from the first patient), the following documents must be available to Novo Nordisk:

- Curricula vitae of Investigator and Sub-investigator(s) (current, dated and signed and/or supported by an official regulatory document)
- Signed and dated agreement on the final protocol
- Financial agreement(s) including physician contract

21 Responsibilities

The Investigator is accountable for the conduct of the study. If any tasks are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties.

The Investigator will follow the instructions from Novo Nordisk when processing data.

The Investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Investigator will prevent any unauthorised access to data or any other processing of data against applicable law.

Upon request from Novo Nordisk, the Investigator will provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that such technical and organisational safety measures have been taken.

22 Reports and Publications

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk for regulatory purposes and for the general development of the drug and the indication. All information supplied by Novo Nordisk in connection with this observational study
shall remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this study. The information obtained during this observational study may be made available to other if deemed necessary by Novo Nordisk.

An Investigator will be designated with the responsibility to review and sign the Observational Study Report (Signatory Investigator).

22.1 Communication and Publication

Novo Nordisk commits to communicating or otherwise making available for public disclosure results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or by other means.

Novo Nordisk reserves the right not to release data until specified milestones, e.g. an Observational Study Report is available. This includes the right not to release interim results from observational studies, because such results may lead to conclusions that are later shown to be incorrect.

At the end of the study, one or more manuscripts for publication will be prepared in collaboration between Investigator(s) and Novo Nordisk. Novo Nordisk will not suppress or veto publications; however Novo Nordisk reserves the right to postpone publication and/or communication for a short time to protect intellectual property.

22.1.1 Authorship

Authorship of publications should be in accordance with guidelines from ICMJE’ Uniform Requirements (sometimes referred to as the Vancouver Criteria).²

22.1.2 Publication(s)

Results from this study will be reported by Novo Nordisk A/S on a publicly available database in compliance with the recommendations issued by ICMJE² and the international pharmaceutical industry association.

In all cases, the study results shall be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the Investigators' and Novo Nordisk's opinions shall be fairly and sufficiently represented in the publication.
In a multi-centre study based on the collaboration of all study sites, any publication of results must acknowledge all study sites.

Novo Nordisk maintains the right to be informed of any Investigator plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

22.1.3 Site-Specific Publication(s) by Investigator(s)

For a multi-centre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients, and therefore may not be supported by Novo Nordisk. It is Novo Nordisk's policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the study.

Novo Nordisk reserves the right to prior review of such publication and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

22.2 Investigator Access to Data and Review of Results

As owners of the study database, Novo Nordisk has discretion to determine who will have access to the database. Generally, study databases are only made available to regulatory authorities.

Individual Investigator(s) will have their own research participants' data.

23 Retention of Observational Study documentation

Patient notes must be kept for the maximum period permitted by the hospital, institution or private practice.

Novo Nordisk will comply with all the requirements of GPP related to archiving of study documentation. Records containing patient sensitive data shall not be archived by Novo Nordisk, but shall be kept with investigator and patient, or local regulations pertaining to personal data protection. The Investigator must agree to archive the documentation pertaining to the study in an archive after completion or discontinuation of the study if not otherwise notified. The Investigator should not destroy any documents without prior permission from Novo Nordisk.

Novo Nordisk must archive study-related documentation for at least five years after final observational study report or first publication of study results, whichever comes later.
24 Indemnity Statement

Novo Nordisk carries product liability for its products and liability assumed under the special laws, acts and/or guidelines for conducting clinical studies in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability by the clinics or doctors conducting experiments or by persons for whom the said clinic or doctors are responsible.

Novo Nordisk accepts liability in accordance with local laws.

25 References


2 NovoSeven® Product Information including Summary of Product Characteristics and Product Label. 2014.


7 International Committee of Medical Journal Editors (ICMJE): Uniform Requirements for Manuscripts Submitted to Biomedical Journals: writing and editing for biomedical publication. Haematologica 2004; 89(3):264.