NON-INTERVENTIONAL STUDY PROTOCOL

FEIBA NF - FACTOR VIII INHIBITOR BY-PASSING ACTIVITY NANOFILTERED

FEIBA NF GLOBAL OUTCOME STUDY

(FEIBA-GO)

PROTOCOL NUMBER: 091301

AMENDMENT 2 GLOBAL VERSION: 2017 DEC 19

Replaces

AMENDMENT 1 (Global): 2015 MAR 25

ALL VERSIONS:

Amendment 2 (Global): 2017 DEC 19
Amendment 1 (Global): 2015 MAR 25
Original: 2013 SEP 30

Study Sponsor: Baxalta Innovations GmbH
Industriestrasse 67
A-1221-Vienna, AUSTRIA

Authorized Representative (Signatory)

[redacted], MD
[redacted],
Global Clinical Development Operations
Baxalta US Inc/ Baxalta Innovations GmbH

Sponsor's Medical Expert

[redacted], MD
[redacted]
Shire, Zug, Switzerland

Study Monitoring

Synteract HCR
Keizer Karellaan 576, PO Box 4
1082 Brussels, Belgium
Tel: [redacted]
Fax: [redacted]

TITLE PAGE - PASS INFORMATION

PROTOCOL TITLE	**FEIBA NF GLOBAL OUTCOME STUDY (FEIBA-GO)**
PROTOCOL ID #	091301
AMENDMENT	**Amendment 2**: 2017 DEC 19 Replaces **Amendment 1: 2015 MAR 25**
EU PAS REGISTER #	Not applicable
MEDICINAL PRODUCT	
Active Ingredient(s)	Anti-Inhibitor Coagulant Complex (AICC) Factor Eight Inhibitor Bypassing Activity Nanofiltered (FEIBA NF);
Medicinal Product	Factor Eight Inhibitor Bypassing Activity Nanofiltered (FEIBA NF)
PRODUCT REF. #	AT/H/0343/001-002
MARKETING AUTHORISATION HOLDER (MAH)	Baxter AG, Industriestrasse 67 A-1221 Vienna, Austria
JOINT PASS	No
RESEARCH QUESTION & OBJECTIVES	
Research Question	
The study addresses the need to measure long-term effectiveness, safety and quality of life outcome measures for haemophilia A or B patients with high-responding inhibitors treated on-demand and in prophylaxis with FEIBA NF. The purpose of the study is to document the natural history of hemophilia A or B disease in subjects with high responding inhibitors either to Factor VIII or Factor IX and to describe long-term outcomes in terms of effectiveness, safety and quality of life in subjects receiving FEIBA NF in routine clinical practice.	
Primary Objective	
1. Describe the hemostatic effectiveness of FEIBA NF in a variety of clinical settings including on-demand therapy, prophylaxis and Immune Tolerance Induction (ITI) in haemophilia A or B patients with high-responding inhibitors	
Secondary Objectives	
1. Describe joint functionality outcomes in subjects receiving FEIBA NF 2. Describe the safety of FEIBA NF 3. Describe the health-related quality of life (HRQoL) 4. Describe acute and chronic pain associated with hemophilia 5. Describe the daily activity level 6. Describe the Health resource use 7. Describe individual pharmacodynamic properties (PD) of FEIBA NF by thrombin generation assay (TGA) 8. Describe FEIBA NF use in different clinical settings	
COUNTRIES OF STUDY	Countries not yet identified
AUTHOR	[redacted]

MARKETING AUTHORIZATION HOLDER(S)

MAH	Baxter AG, Industriestrasse 67 A-1221 Vienna, Austria
MAH CONTACT PERSON	[redacted]

SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs), to the ethics committee(s) (ECs).

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE RESPONSIBLE PARTY WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

See SAER form for contact information.
Further details are also available in the study team roster.

For information on the assessment and definitions of these events refer to: assessment of AEs in Section 11.1 and definitions of AE in Section 11.2, SAE in Section 11.2.2.

NON-SERIOUS ADVERSE EVENT REPORTING

Non-serious Adverse Events (NSAEs) should be entered onto the CRF within 5 working days.

1. TABLE OF CONTENTS

Tables

2. LIST OF ABBREVIATIONS AND GLOSSARY

Abbreviation	Definition
ABR	annualized bleed rate
ADL	Activity of Day Living
AE	adverse event
AICC	anti-inhibitor coagulant complex
APCC	activated prothrombin complex concentrates
aPTT	activated partial thromboplastin time
B19V	parvovirus B19
BPA	by-passing agent
BU	Bethesda unit
BW	body weight
CRF	case report form
Chronic pain	continuous and/or intermittent pain, related to the pathophysiology of haemophilia, requiring intervention (pharmacological or non-pharmacological treatment), and in which the cause of pain cannot be readily removed, occurring more than once a week and lasting 3 months or more [1]
DIC	disseminated intravascular coagulation
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ER	emergency room
ETP	endogenous thrombin potential
FEIBA	Factor Eight Inhibitor Bypassing Activity
FEIBA NF	Factor Eight Inhibitor Bypassing Activity Nanofiltered
FVIIa	activated factor VII
FVIII	factor VIII
FIX	factor IX
GPV	Global Pharmacovigilance
HAL	Haemophilia Activities List [2,3]
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
High responding inhibitors:	inhibitors with peak activity >5 Bethesda Units (BU/ml) at any time associated with anamnesis following replacement of the missing clotting factor [4,5]
HIV	human immunodeficiency virus
HJHS	Haemophilia Joint Health Score

Abbreviation	Definition
HRQoL	Health-Related Quality of Life
HRUR	health resource used related
ICF	informed consent form
IQR	inter quartile range
ITI	immune tolerance induction
MAH	marketing authorization holder
MBR	monthly bleed rate
MRI	magnetic resonance imaging
NMC	non-medical complaint
NRS	numerical rating scale
NSAE	non-serious adverse event
On-demand treatment	treatment of acute bleeds with any factor concentrates with the goal to resolve bleeds
PD	pharmacodynamic(s)
PedHAL	Pediatric Haemophilia Activity Level
Prophylaxis	Regular administration of factor concentrates with the goal to prevent bleeds. For analysis purposes, in this protocol, prophylaxis is defined as follows: • continuous prophylaxis (>46 weeks; long-term) [6] • intermittent prophylaxis (>12 weeks-46 weeks) • episodic prophylaxis (≤12 weeks) • peri-Immune Tolerance Induction (ITI) prophylaxis For analysis purposes FEIBA prophylaxis is defined as at least three administrations per week [6]
QoL	quality of life
RoM	range of motion
SAE	serious adverse event
SAER	serious adverse event report
SAP	statistical analysis plan
SIC	subject identification code
TAE	thrombotic adverse event
Target Joint	≥3 hemarthroses in any single joint during a 6-month period [7]
TG	thrombin generation
TGA	thrombin generation assay
VAS	Visual Analog Scale
vs.	versus
WFH	World Federation of Haemophilia

3. RESPONSIBLE PARTIES

3.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted],
Global Clinical Development Operations
Baxalta Innovations GmbH , Vienna, Austria

3.2 Investigator(s)

Steering Committee	[redacted], [redacted] (Spain)
	[redacted], [redacted] (Germany)
	[redacted], [redacted] (Belgium)
	[redacted], [redacted] (Norway)
	[redacted], [redacted] (France)
	[redacted], [redacted] (UK)
	[redacted], [redacted] (Italy)
	[redacted], [redacted] (Poland)

The name and contact information of the investigators involved with the study will be maintained separately by the responsible party.

4. ABSTRACT

Title: FEIBA-GO - FEIBA NF GLOBAL OUTCOME STUDY

Version: Protocol Amendment 2 19 DEC 2017

Study Medical Director:
[redacted], MD
[redacted]
Shire, Zug, Switzerland

Rationale and background:

This study will be a post-authorization, prospective, uncontrolled, observational, open-label, non-interventional, multicenter cohort study to describe the natural history of haemophilia A or B with high-responding inhibitors [4,5] to factor VIII or IX and long-term outcomes in terms of effectiveness, safety and quality of life in subjects receiving Factor Eight Inhibitor Bypassing Activity Nanofiltered (FEIBA NF) in different settings in routine clinical practice.

Research question and objectives:

The purpose of the study is to document the natural history of haemophilia A or B disease in subjects with high-responding inhibitors either to Factor VIII or Factor IX and to describe long-term outcomes in terms of effectiveness, safety and quality of life in subjects receiving FEIBA NF in routine clinical practice.

The primary objective is to describe the hemostatic effectiveness of FEIBA NF in a variety of clinical settings including on-demand therapy, prophylaxis and ITI in haemophilia A or B patients with high-responding inhibitors.

The secondary objectives are aimed at describing:

- Joint functionality outcomes in routine clinical practice
- Safety of FEIBA NF
- Health-related quality of life (HRQoL)
- Acute and chronic pain associated with haemophilia
- Daily activity level
- Health resource use
- Individual pharmacodynamic (PD) properties of FEIBA NF by thrombin generation assay (TGA)
- FEIBA NF use in different clinical settings

Study design:

This study will be a post-authorization, prospective, uncontrolled, observational, non-interventional, open-label, multicenter cohort study. Treatment regimens will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. Visits to the investigator and all other medical care will be performed as is standard for the site and for the subject´s healthcare. The observation period for each enrolled subject will be 4 years.

Population:

Male haemophilia A or B patients with high-responding inhibitors who had been prescribed FEIBA NF for the treatment or prevention of bleeding events by a treating physician prior to the decision to enroll in the study.

Inclusion criteria:

Subjects of any age who meet **ALL** of the following criteria are eligible for this study:

- Subject is a male congenital haemophilia A or B patient with high-responding inhibitor of any titer diagnosed before study entry
- Subject has been prescribed treatment with FEIBA NF as part of routine clinical practice, either on-demand or prophylactic treatment or during ITI

Exclusion criteria:

Subjects who meet **ANY** of the following criteria are not eligible for this study:

- Subject has a known hypersensitivity to the product or any of its components
- Subject has other contraindications to FEIBA NF: FEIBA NF must not be used in the following situations if therapeutic alternatives to FEIBA NF are available:
  - Disseminated intravascular coagulation (DIC)
  - Thromboembolic events (e.g., Myocardial infarction, Stroke, TIA, DVT, PE)
- Subject has any other severe concomitant clinically relevant bleeding disorder
- Subject has participated in another interventional clinical study involving a medicinal product or device within 30 days prior to enrollment or is scheduled to participate in another interventional clinical study involving a medicinal product or device during the course of this study
- Subject is a family member or employee of the investigator

Data sources:

Data will be prospectively collected at the centers and recorded onto case report forms (CRFs) from hospital medical records and the subject diaries completed by the subjects or their legally authorized representatives at home .

Study size:

Approximately 55 evaluable subjects are planned to be included in the study. As no hypothesis testing or interval estimation will be applied, the sample size for the study is not based on statistical considerations.

Data analysis:

Descriptive statistics will include specifically but not exclusively, arithmetic mean, standard deviations, medians, minimum, maximum, 25th and 75th percentiles, proportions, frequency counts and 95% confidence intervals of select point estimates. Figures will be prepared to illustrate the patterns of data over time where appropriate.

Milestones:

First subject in (start of data collection): 03 September 2014
Last subject out (end of data collection): 31 Dec 2021
Interim Study Report 1 (enrollment completed): 31 May 2018
Interim Study Report 2 : 31 May 2019
Interim Study Report 3: 31 May 2020
Interim Study Report 4: 31 May 2021
Final Study Report (all subjects with completed follow-up): 30 May 2022

5. AMENDMENTS AND UPDATES

Amd. No.	Date	Section of Protocol	Amendment	Reason
1	2015 MAR 25	Throughout the protocol	Refer to Section 14.4 for the Summary of Changes	Administrative
2	2017 DEC 19	Throughout the protocol	Refer to Section 14.4 for the Summary of Changes	

6. MILESTONES

Milestone	Planned Date
Start of data collection (first subject in [FSI])	03 SEP 2014
End of data collection (last subject out [LSO])	31 Dec 2021
Study Progress Report	With every PSUR
Interim Study Report 1	31 May 2018
Interim Study Report 2	31 May 2019
Interim Study Report 3	31 May 2020
Interim Study Report 4	31 May 2021
Registration in EU PAS Register	EUPAS6691
Final Study Report	30 May 2022

7. RATIONALE AND BACKGROUND

7.1 Critical Review of Available Data

Haemophilia represents a rare X-linked genetic disorder of primary haemostasis, caused by either deficiency in coagulation factor VIII (haemophilia A), or coagulation factor IX (haemophilia B). Haemophilia A affects 1-2 in 10,000 male newborns across all ethnic groups. Haemophilia B is even rarer, with 1-2 in 50,000 male newborns affected.[8] Individuals with severe deficiency require life-long coagulation factor replacement therapy, for treatment or prevention of spontaneous or traumatic bleeds.

One of the most serious complications of replacement therapy is the development of inhibitory antibodies against the exogenously applied coagulation factor in as many as 20-30% of patients with severe haemophilia A, and in 1-5% of patients with severe haemophilia B. Inhibitory antibodies also occur in a small percentage of patients with mild or moderate haemophilia A. The development of inhibitors is a serious complication of haemophilia.[9] The risk for inhibitor development to FVIII depends on a number of factors relating to the characteristics of the patient, including: causative FVIII gene mutations, family history of inhibitors, ethnicity, intensity of treatment, and the early implementation of prophylactic treatment.[10,11,12] A substantial proportion of patients with FVIII inhibitors have high responding, high titer inhibitors [> 5 Bethesda units (BU)].

Both available by-passing agents (BPA) AICC and rFVIIa are able to control acute hemorrhages in hemophilia patients with high titer inhibitors. These agents control bleeding by promoting the conversion of prothrombin to thrombin with subsequent fibrin polymerization and clot formation via mechanisms that do not require FVIII. It has been proposed that AICC achieves this goal principally by virtue of the presence of a “partial prothrombinase complex” consisting of activated factor X (FXa) and prothrombin.[13]

Hemophilia patients with high-titer inhibitors experience severe and recurrent bleeds in joints, muscles, and soft tissues leading to significant joint damage and morbidity. These patients are at increased risk for bleedings that are difficult to control. Poorly controlled hemarthroses result in the early onset of chronic joint disease and physical disability, which can substantially impair the quality of life (QoL) of patients.[14] Prophylaxis, the routinely scheduled replacement of factor VIII, is standard care for patients who have severe haemophilia A without inhibitors, because of its ability to prevent bleeding.[15,16,17,18,19] Patients with inhibitors with refractory bleeding may have an even greater benefit from prevention of bleeding compared to haemophilia patients without inhibitors. This hypothesis is supported by literature from retrospective reviews, case study reports, observational and randomized studies indicating that prophylactic treatment of these patients with AICC or rFVIIa may reduce the morbidity and improve general health [20,21,22,23,24,25,26] and Health-Related Quality of Life (HRQoL).[15,27,28,29,30]

In 2011 results from the ProFEIBA study [7], the first prospective, randomized, crossover study on FEIBA/FEIBA NF in prophylaxis vs. on-demand were published . This study compared 6 months of AICC prophylaxis at a target dose of 85 U (±15%) per kilogram of body weight (BW) on 3 nonconsecutive days per week, with 6 months of on-demand therapy for bleeding episodes at the target dose of 85 U/kg BW (±15%). Between the two treatment regimens in this cross-over design, there was a 3-month washout period, during which patients received on-demand therapy for bleeding episodes. During the prophylaxis period, the mean (±SD) number of bleeds was 5.0±5.0, as compared to 13.1±7.1 during the on-demand period (P<0.001), representing a 62% reduction in total bleeding events. For the 16 patients in whom bleeding episodes were reduced by 50% or more during prophylaxis, the overall reduction in the bleeding rate was 84%, and 6 of these patients did not experience any bleed during the prophylaxis period. Target-joint bleeds were reduced by 72% during the prophylaxis period as compared with the on-demand period (P<0.001).

In August 2013, the results of Baxter's "PROOF" prospective, randomized, parallel study designed to evaluate efficacy and safety of prophylactic versus on-demand treatment with FEIBA NF in subjects with haemophilia A or B and a high titer inhibitor were published.[31] These new data confirm that FEIBA NF prophylaxis is effective, compared to an on-demand regimen: in fact, a 72.5% lower median annualized bleeding rate (ABR) was observed (28.7 ABR during FEIBA NF on-demand treatment as compared to 7.9 ABR during FEIBA NF prophylactic treatment).[31] The PROOF study adds to the clinical evidence supporting the prophylactic use of FEIBA NF. The prophylactic dose administered in the PROOF study was similar (85 ± 15 U/kg BW, i.e. 70-100U/kg BW) to the target dose in the ProFEIBA study (85 U/kg BW ± 15%; i.e. 72 – 98 U/kg BW), however, the two trials differ in the design (parallel arms vs. cross-over), in the regimen (every other day vs. 3 non-consecutive days weekly) and in the duration of follow-up (one year vs. six months).

The FEIBA GO study introduced in this protocol is intended to collect more evidence in order to address the following clinical research questions:

- Prevention of bleeds can preserve the status and functionality of patient's joints or significantly delay the onset of joint damage, particularly if prophylaxis is started at an early age or even in case of secondary or tertiary [32] prophylaxis when some damage is already present in the joints. Tracking patient outcomes over a longer period of time on prophylaxis will enable to follow the evolution of joint status and function over time in the FEIBA GO study.

- Data on prophylaxis from the randomized ProFEIBA and PROOF studies [7,31] are consistent, but the question on the optimal prophylactic regimen remains open. The FEIBA GO study aims at collecting data on efficacy of different FEIBA NF regimens used in common practice for the prophylactic treatment of inhibitor patients.
- In both the ProFEIBA [7] and PROOF [31] study some patients appeared to respond better than others to the treatment with the prophylactic regimens used. The FEIBA GO study will provide the opportunity to observe whether individually tailored treatment regimen changes can further improve patient outcomes and result in an additional reduction of bleeding events.
- The FEIBA GO study will also allow to collect data from routine clinical practice on larger number of inhibitor patients regarding health resource use, quality of life, number of days lost from school or work due to bleeding episodes, and the possible correlation between TGA and clinical outcome.
- The FEIBA GO study may also help to identify subgroups of patients that can benefit most from prophylaxis treatment, which is of great importance in a complex clinical situation such as the presence of high responding inhibitors to FVIII or FIX in haemophilia patients.
- The FEIBA GO study will also allow to collect safety data from routine clinical practice regarding the safety of FEIBA NF and to explore the possible difference in safety profile of FEIBA used on-demand vs. prophylactically

7.2 Medicinal Product Safety Profile

Overall, FEIBA NF was well tolerated as reported in Baxter internal studies and in published clinical evidence. No thrombotic complication was reported in two prospective, clinical trials on prophylaxis (ProFEIBA [7] and PROOF [31,i;ii]). One thrombotic event deemed to be possibly related to FEIBA was reported in a prospective study on FEIBA use for surgery (SURF study).[33]

The safety of FEIBA with regard to thrombotic adverse events, the major concern with all bypassing agents, was reviewed specifically in two publications.[34,35]

Ehrlich et al. (2002)[34] analysed adverse event (AE) data that had been reported spontaneously to the pharmacovigilance department at Baxter BioScience. The database also included AE reports identified through screening of current literature.

[i] FEIBA NF 090701 Clinical Study Report, dated 14 Jan 2013, Table 10
[ii] FEIBA NF 090701 Clinical Study Report dated 14 Jan 2013, Section 12.2.3.2.1, page 76

Over a 10-year period, altogether 55 events of all types had been reported. Among them, 16 thrombotic AEs (29%) were documented, relating to Disseminated Intravascular Coagulation (DIC), acute myocardial infarction, pulmonary embolism and thromboses. There was a single fatality. The observed reporting rate of total thrombotic AEs for the compilation period was approximately 4 per 100,000 infusions. Known risk factors were evident in 81% of the patients with thrombotic events. The findings provide encouragement that the risk of thrombotic complications in patients receiving FEIBA is low.

Aledort (2004) [35] reviewed MedWatch (the United States FDA pharmacovigilance system) data on thrombotic complications for both FEIBA and rFVIIa between April 1999 (i.e. the time when rFVIIa was introduced for clinical use in the USA) and June 2002. It was concluded that thrombotic AEs following either FEIBA or rFVIIa are rare. Similar to the publication by Ehrlich et al. (2002), risk factors were identified in the vast majority of patients with thrombotic AEs. Documented experience also provides assurance that in the majority of patients with FVIII or FIX inhibitors, FEIBA achieves comparable hemostatic efficacy as would be expected in non-inhibitor patients treated with coagulation factor replacement therapy.

In 1983, Hilgartner et al.[36] examined the efficacy and safety of FEIBA in the treatment of joint, mucous membrane, musculocutaneous and emergency bleeding episodes in a multicentre, uncontrolled clinical study. In 49 patients with inhibitor titres >5 BU, 489 infusions were given for the treatment of 165 bleeding episodes. Of the 489 infusions, 18 (3.7%) caused minor transient reactions in recipients, which included chills, fever, nausea, dizziness and unusual taste in mouth. No SAEs were reported. An anamnestic response to FVIII was observed in 10 of 49 patients (20%); however, anamnesis was not observed to interfere with the efficacy of FEIBA.

A subsequent prospective, multicentre study [37] examining the safety and efficacy of FEIBA was conducted following the introduction of the vapour heat treatment to the AICC manufacturing process. In this study, 41 patients with haemophilia and inhibitors were treated with FEIBA for 106 bleeding episodes. Of the 328 total infusions administered, 7 minor adverse reactions were reported, including minor chest pain and tightness, drowsiness, and discomfort of breathing. No SAEs were reported.

The safety and efficacy of FEIBA during home treatment was examined by Négrier et al. (1997) [38] and Glomstein et al. (2002) [39] in 2 prospective studies in France and Norway, respectively. In the French home treatment study, 10 patients were treated with FEIBA for 134 bleeding episodes. No adverse events were observed during the study.

Ninety-six percent of 134 episodes treated with FEIBA were rated excellent or good. In the Norway home treatment study, 6 patients were treated with 100 infusions of FEIBA. No adverse events were observed during the study.

A post-marketing surveillance study was carried out in 2006 by DiMichele and Negrier [20] to increase comprehension of the full therapeutic profile of FEIBA by evaluating its safety and efficacy in the settings of acute bleeding, surgery, and prophylaxis. Data collection booklet packets were distributed in 1999 to treatment centers and hospitals in the United States (n = 30) and Europe (n = 42); responses were received from 53% and 57% of the centers, respectively. The overall response rate was 56%, with data collected on 79 patients, but the final sample size comprised 63 inhibitor patients with either haemophilia A or B. Information was available for 200 FEIBA treatment periods and included data on >4.500 infusions. Twelve patients were in more than one treatment group. Physicians were asked to provide details for cases in which treatment with FEIBA was well documented and occurred between 1995 and 2001, inclusive. Efficacy was determined by a global assessment. Tolerability was assessed via reports of adverse events (AEs) during treatment with FEIBA. A total of two AEs during 204 FEIBA treatment periods (<1%) and more than 4.500 infusions (<0.04%) were reported. FEIBA - related AEs were reported in a single patient with haemophilia A on two separate occasions. The patient developed hives after FEIBA administration for a forearm bleed and later developed bronchial spasms, despite pretreatment with diphenhydramine, for the treatment of a soft tissue foot bleed. Efficacy was assessed as fair and good for the first and second treatments, respectively. No AEs were reported during the course of surgical or musculoskeletal prophylactic treatment with FEIBA. No thrombotic events were reported in any of the treatment groups.

In August 2013, the results of Baxter's "PROOF" prospective, randomized, parallel study designed to evaluate efficacy and safety of prophylactic versus on-demand treatment with FEIBA NF in subjects with haemophilia A or B and a high titer inhibitor were published.[31] Among the 36 treated subjects, no thromboembolic events or major safety issues were identified. Furthermore, an evaluation of laboratory markers of thrombogenicity did not reveal any apparent trends over time.

Consensus panels have developed recommendations on assessing haemostasis and dosing of bypassing agents.[40] For FEIBA, the dosages recommended in the Package Insert Leaflet have shown over the years to be adequate, and thus represent the basis for the published consensus statement.

For additional information, please refer to the Package Insert Leaflet.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The study addresses the need to measure long-term effectiveness, safety and quality of life outcomes for haemophilia A or B patients with high-responding inhibitors [4,5] treated on-demand and in prophylaxis [6] with FEIBA NF. The purpose of the study is to document the natural history of hemophilia A or B disease in subjects with high responding inhibitors either to Factor VIII or Factor IX and to describe long-term outcomes in terms of effectiveness, safety and quality of life in subjects receiving FEIBA NF in routine clinical practice.

8.2 Primary Objective

The primary objective of the study is to describe the hemostatic effectiveness of FEIBA NF in a variety of clinical settings including on-demand therapy, prophylaxis and ITI in haemophilia A or B patients with high-responding inhibitors.

8.3 Secondary Objectives

The secondary objectives of the study are to describe:

- Joint functionality outcomes in subjects receiving FEIBA NF
- Health-related quality of life (HRQoL)
- Acute and chronic pain associated with hemophilia
- Daily activity level
- Health resource use
- Individual pharmacodynamic properties (PD) of FEIBA NF by TGA
- FEIBA NF use in different clinical settings
- Safety of FEIBA NF

9. RESEARCH METHODS

9.1 Study Design

This study will be a post-authorization, prospective, uncontrolled, observational, non-interventional, open-label, multicenter cohort study to describe the natural history of haemophilia A or B with high-responding inhibitors and long-term outcomes in subjects receiving FEIBA NF in routine clinical practice in different settings including prophylaxis, on-demand and ITI in terms of effectiveness, safety and quality of life.

Approximately 55 evaluable patients are planned to be included in the study. Subjects may be of any age. Subjects must have been prescribed FEIBA NF for the treatment or prevention of bleeding events by the treating physician before study participation.

Data for individual subjects will be collected over a period of 4 years for each enrolled subject.

The treating physicians will determine the treatment regimen, as well as the frequency of laboratory, radiologic, and clinical monitoring. Study visits are to coincide with routinely scheduled and emergency visits. Available data from these visits shall be recorded onto the case report forms (CRFs). The protocol does not require any additional testing or monitoring beyond what is deemed necessary by the treating physician. It is considered standard practice for haemophilia patients with inhibitors to maintain a diary which captures treatment with BPA and also Factor VIII products (e.g. for ITI) and disease-related data. A subject diary will be provided to each subject to help with the standardization of data collection. Nevertheless, the completion of the diary is a voluntary effort by the individual subject or subject's legally authorized representative.

All adverse events (AEs) and number of bleed occurrences recorded in the subject diary during study participation period will be recorded onto the CRFs. For other types of data in the subject diary, such as pain and effectiveness assessments, the investigator shall determine, at the beginning of the study, whether or not the level of completeness in record keeping and overall subject compliance is adequate. HRQoL questionnaires will also be provided at the screening visit and at interval visits to subjects or subjects' legally authorized representatives who opt to voluntarily complete them.

9.1.1 Primary Endpoints

Hemostatic and Preventative Efficacy

The primary objective to describe the hemostatic effectiveness of FEIBA-NF in haemophilia A or B patients with high responding inhibitors will be assessed as follows:

- For treatment of bleeding episodes in subjects on on-demand and for breakthrough bleeds in subjects on prophylaxis treatment
  - Annualized bleeding rate (ABR) and/or monthly bleeding rate (MBR), all bleeds
  - ABR or MBR, all joint bleeding events
  - Total number of infusions of FEIBA NF required to control bleeds
  - Total weight adjusted dose (U/kg) of FEIBA NF required to control bleeds
  - Total units infused (U) of FEIBA NF required to control bleeds
  - Assessment of effectiveness:
    - Total number (%) of treated bleeds and their corresponding hemostatic efficacy ratings using an "excellent-to-poor" 4-point Likert scale by the subjects or caregiver for treatments given at home or by the investigator for treatments given in the hospital/clinic.
- For prevention of bleeding episodes :
  - Annualized bleeding rate (ABR) and/or monthly bleeding rate (MBR), all bleeds
  - ABR or MBR, all joint bleeding events
  - Assessment of effectiveness:
    - Total number (%) of bleeding episodes with corresponding hemostatic efficacy ratings with an "excellent-to-poor" 4-point scale by the subjects or care-giver at the end of each prophylaxis period (possibly rated within 24 hours from the end of the prophylactic treatment) or on an annual basis depending on which occurs first.
  - Total units infused (U), total weight adjusted dose (U/kg), and total number of infusions of FEIBA NF.

9.1.2 Secondary Endpoints

9.1.2.1 Joint Health/Function Outcomes

- Joint clinical outcomes in routine clinical practice setting, using any therapeutic regimen, assessed as in common practice, by:
  - WFH Orthopedic Joint Score (Gilbert scale) and Haemophilia Joint Health Score (HJHS)
  - X-ray using Pettersson scale
  - Magnetic Resonance Imaging (MRI) and or ultrasound scanning
  - Number of total target joints (defined as 3 or more bleeds in the same joint in a 6-month period [7])
  - Number and reason of invasive surgical procedures, such as (but not exclusively) orthopedic surgery, radiosynovectomy and chemosynovectomy Number of breakthrough bleeding events in patients on prophylaxis and number of consecutive months on prophylaxis

9.1.2.2 Health-Related Quality of Life

- HRQoL, assessed by (if all or any of the below is available):
  - SF-12v2 and EQ-5D questionnaires – for adult subjects >18 years
  - SF-10, for pediatric subjects aged 4-13 years
  - EQ-5D-Y, for pediatric subjects aged 7-17 years and it can be parent-completed
- Chronic pain [defined as "Continuous and/or intermittent pain, related to the pathophysiology of haemophilia, requiring intervention (pharmacological or non-pharmacological pain treatment), in which the cause of pain cannot be readily removed, occurring more than once a week and lasting 3 months or more"] [7] associated with hemophilia, if available, assessed by
  - Numeric Rating Scale (NRS)
  - Pediatric "Wong Baker Face Scale"
- Acute pain associated to haemophilia assessed by, if available
  - Numeric Rating Scale (NRS)
  - Pediatric "Wong Baker Face Scale"

- Daily activity level, if available, assessed by
  - Haemophilia Activity Level scale (HAL) in adults and
  - Pediatric Haemophilia Activity Level scale (PedHAL) in children aged 8-17 years

9.1.2.3 Other Secondary Objectives

- Health resource use:
  - Number of visits at the site
  - Unscheduled visits at the site
  - Number of hospitalizations related to haemophilia (surgery excluded)
  - Length of stay in hospital per stay (number of days)
  - Number of days lost from school or work by patients and caregivers due to bleeding episodes
  - Antiphlogistic drug use
- Individual pharmacodynamic (PD) properties of FEIBA NF assessed by
  - Thrombin generation assay (TGA), if available

9.1.2.4 Safety

- Incidence, severity and relatedness of serious adverse events (SAE)
- Incidence, severity and relatedness of non-serious adverse events (NSAE)
- Incidence, severity and relatedness of thromboembolic events and thrombotic microangiopathy (TMA events) (refer to Section 11.2.2)
- Incidence in safety profile of FEIBA used on-demand and prophylactically based on assessment of all SAEs in the respective sub-group

9.2 Setting

9.2.1 Medicinal Product

FEIBA NF is formulated as a sterile white, off-white or pale green powder and solvent for solution for infusion. As the active ingredient, FEIBA NF 500 U contains 500 U factor VIII inhibitor bypassing activity in 200 – 600 mg human plasma protein. FEIBA NF 1000 U contains 1000 U factor VIII inhibitor bypassing activity in 400 – 1200 mg human plasma protein. FEIBA NF 2500 U contains 2500 U factor VIII inhibitor bypassing activity in 1000 – 3000 mg human plasma protein. FEIBA NF also contains the factors II, IX and X, mainly in non-activated form, as well as activated factor VII.

Factor VIII coagulation antigen (F VIII C:Ag) is present at a concentration of up to 0.1 U./1 U. FEIBA NF. The factors of the kallikrein-kinin system are present in trace amounts only, if at all. 1 unit of FEIBA NF shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma by 50% of the buffer value (empty value).

Dosage and duration of treatment depend on the severity of the hemostatic disorder, the localization and the extent of the bleeding, as well as the clinical condition of the patient. Dosage and frequency of administration should always be guided by the clinical efficacy in each individual case. As a general guideline, a dose of 50 –100 U FEIBA NF per kg BW is recommended; a single dose of 100 U/kg BW and a maximum daily dose of 200 U/kg BW must not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses. FEIBA NF treatment regimen will be determined by the treating physician.

Paediatric use (children)

The experience in children under 6 years of age is limited; the same dose regimen as in adults should be adapted to the child's clinical condition.

Special precautions for storage

Do not freeze. Store in the original package in order to protect from light. For storage conditions of the reconstituted medicinal product see the FEIBA NF SPC / Package Insert

Method of administration

Reconstitute the product (see the FEIBA NF SPC / Package Insert) and slowly inject or infuse via the intravenous route . An infusion rate of 2 U/kg BW per minute must not be exceeded. Chemical and physical in-use stability has been demonstrated for 3 hours at room temperature. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination (controlled and validated aseptic conditions), the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Reconstituted product must not be refrigerated.

9.2.2 Duration of Study Period and Subject Participation

The overall duration of the study is expected to be approx.7 years from the study initiation (i.e. first subject enrolled) to study completion (i.e. last subject last visit). The recruitment period is planned to be approx.3 years. The subject participation period is 4 years from enrollment to study completion (i.e. last study visit) unless prematurely discontinued for whatever reason.

9.2.3 Subject Selection Criteria

Subjects must have been prescribed FEIBA NF for the treatment or prevention of bleeding events by a treating physician prior to the decision to enroll in the study.

No additional diagnostic or monitoring procedures may be applied to subjects, except those that are part of normal/routine clinical practice.

9.2.3.1 Inclusion Criteria

Subjects of any age who meet **ALL** of the following criteria are eligible for this study and who are willing and able to comply with the requirements of the protocol:

- Subject is a male congenital haemophilia A or B patient with high-responding inhibitor of any titer diagnosed before study entry
- Subject has been prescribed treatment with FEIBA NF as part of routine clinical practice, either on-demand, as prophylactic treatment or during ITI

9.2.3.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

- Subject has a known hypersensitivity to the product or any of its components
- Subject has other contraindications to FEIBA NF: FEIBA NF must not be used in the following situations if therapeutic alternatives to FEIBA NF are available:
  - Disseminated intravascular coagulation (DIC)
  - Acute thrombosis or embolism (including myocardial infarction)
- Subject has any other severe concomitant clinically relevant bleeding disorder
- Subject has participated in another clinical study involving a medicinal product or device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving a medicinal product or device during the course of this study.
- Subject is a family member or employee of the investigator

9.2.4 Informed Consent and Enrollment

Any patient who directly or indirectly through a legally authorized representative provides informed consent (ie, signs and dates the informed consent form - ICF - and assent form, if applicable) is considered enrolled in the study.

9.2.5 Subject Identification Code (SIC)

The following series of numbers will comprise the SIC: protocol identifier (eg, 091301) to be provided by the responsible party, 2- or 3-digit number study site number (eg, 02) to be provided by the responsible party, and 3- or 4-digit subject number (eg, 0003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 091301-020003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

9.2.6 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log will also serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject. As it is common practice for patients to visit site at least once a year, data on recruited subjects are expected to be collected at the enrolment visit and during the screening visit the interval visits at year 2 and 3, and at the termination visit.

Data will be prospectively collected at the sites and recorded onto CRFs from hospital medical records and the subject diaries will be completed by the subjects at home.

Data will be collected at the screening visit and during the interval visits as in routine practice at the centre and registered onto patient diaries at home by the patient or subject's legally authorized representatives.

Details on the procedures to be performed at each study visit, including screening, can be found in Table 1 and in Table 2.

Table 1
Schedule of Study Procedures and Assessmentsa

Procedures / Assessments	Screening Visit	Interval Visits	Termination Visit
Informed Consent[b]	X		
Eligibility Criteria	X		
Medical History	X		
Haemophilia Treatment History	X	X	X
Concomitant Medications	X	X	X
Non-drug Therapies	X	X	X
Physical Examination	X	X	X
Joint Evaluation	X	X[c]	X[c]
Surgical Procedures		X	X
Subject Diary	D	R/D[c]	R
Adverse Events		X	X
Laboratories	X	X	X
Bleeding Episodes and their treatment		X	X
Infusions of FEIBA NF (for bleeding episodes or prophylaxis – refer to glossary)		X	X
Health Resource Use		X	X
QoL Questionnaires	X	X	X
Chronic and acute pain assessment	X	X	X
Daily Activity Level	X	X	X
End of Study Form			X

a. Standard procedures to be performed according to routine practice
b. Occurs at enrolment (before screening)
c. At interval visit only as part of the routine practice

D: Distributed
R: Returned

Table 2
Clinical Laboratory Assessmentsa

Procedures / Assessments	Screening Visit	Interval Visits	Termination Visit
Inhibitor to FIX[b]	X	X	X
Inhibitor to FVIII[b]	X	X	X
TGA[c]	X	X	X

a. Standard procedures performed according to routine practice and if part of the routine prectice
b. Specify inhibitor titer, inhibitor assay methods and reference standard in the CRF
c. Specify laboratory methodology and collection time in the CRF

9.2.7 Subject Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. The data collected on withdrawn subjects will be used in the analysis and included in the clinical study report.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and responsible party have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

9.2.8 Study Stopping Rules

Stopping rules will not be established for this study

9.3 Variables

9.3.1 Efficacy Variables

9.3.1.1 Hemostatic and Preventive Efficacy

The primary objective to describe hemostatic effectiveness of FEIBA NF in haemophilia A or B subjects with high responding inhibitors will be analyzed as follows:

- For treatment of bleeding episodes in subjects on on-demand treatment and for breakthrough bleeds in subjects on prophylaxis treatment
  - Annualized (ABR) and/or monthly bleeding rate (MBR), all bleeds, will be calculated as appropriate, based on the following formula: ABR = (number of bleeds/observational period days)*365.25; MBR = (number of bleeds/observational period - days)*30.44
  - ABR and/or MBR will be calculated as appropriate, in all joint bleeding events
  - Total number of infusions of FEIBA NF required to control bleeds
  - Total weight adjusted dose (U/kg)of FEIBA NF required to control bleeds
  - Total units infused (U) of FEIBA NF required to control bleeds
  - Assessment of effectiveness
    - Total number (%) of treated bleeds and their corresponding hemostatic efficacy ratings using an “excellent-to-poor” 4-point Likert scale by the subjects or caregiver for treatments given at home or by the investigator for treatments given in the hospital/clinic.

Table 3 Overall Effectiveness Assessment for On-Demand Treatment	
Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) within approximately 6 hours to 12 hours and after 1 or 2 infusions. No additional infusion is required for the control of bleeding. Any additional infusion for treatment of bleeding will preclude this rating. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 6 hours to 24 hours requiring more than 2 infusions for complete resolution. Administration of further infusions to maintain hemostasis would not affect this scoring.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding within approximately 6 hours to 24 hours. Requires multiple infusions for complete resolution.
Poor	No improvement of signs or symptoms or conditions worsen.

- For prevention of bleeding episodes:
  - Annualized (ABR) and/or monthly bleeding rate (MBR), all bleeds, will be calculated as appropriate, based on the following formula: ABR = (number of bleeds/observational period days)*365.25; MBR = (number of bleeds/observational period - days)*30.44
  - ABR and/or MBR will be calculated as appropriate, in all joint bleeding events
  - Assessment of efficacy
    - The efficacy will be assessed by a “excellent-to-poor” 4-point Likert scale by the subjects or care-giver at the end of each prophylaxis period (possibly rated within 24 hours from the end of the prophylactic treatment) or on an annual basis depending on which occurs first.

Table 4 Overall Effectiveness Assessment for Prophylaxis Therapy	
Excellent	Definitely low bleeding rate with improvement in daily activities and quality of life. Very satisfied with the treatment and worth being continued-
Good	Relatively low bleeding rate with some improvement in daily activities and quality of life. Satisfied with the treatment and worth being continued-
Fair	Minimal change in breakthrough bleeding episodes with only partial benefit in terms of activity level and quality of life. Partially satisfied with the treatment. Not sure if it is worth continuing treatment
Poor	Frequent breakthrough bleeding episodes interfering with activity level and quality of life. Not satisfied with the treatment.

- Total number of infusions of FEIBA NF
- Total weight adjusted dose (U/kg)of FEIBA NF
- Total units infused (U) of FEIBA NF

9.3.1.2 Joint Health/Function Outcomes

The instruments for the evaluation of the secondary efficacy endpoints (see Section 9.1.2.1) are

- Joint clinical outcomes in routine clinical practice setting, using any therapeutic regimen, assessed as in common practice if available by:
  - WFH Orthopedic Joint Score (Gilbert scale) in adults and Haemophilia Joint Health Score (HJHS) in children or any other measurement system used:
    - The World Federation of Haemophilia developed a musculoskeletal evaluation system, commonly referred to as the Gilbert test, to measure haemophilia joint health status.[41] The Gilbert test needs to be performed in the absence of acute bleed, acute pain, and acute inflammation into the evaluated joint. Gilbert scores of target joints will be collected during screening, intervals, and termination visits or whenever the treating physician deems it appropriate.

Table 5
Gilbert Scale for Musculoskeletal Evaluation of Haemophilic Joints

Pain	0: no pain; no functional deficit; no analgesic use (except with acute hemarthrosis) 1: mild pain; does not interfere with occupation or activities of daily living (ADL); may require occasional non-narcotic analgesic 2: moderate pain, partial or occasional interference with occupation or ADL; use of non-narcotic medications; may require occasional narcotic analgesic 3: severe pain; interferes with occupation or ADL; frequent use of non-narcotic and narcotic analgesic
Bleeding	0: no joint bleed per year 1: no major or 1-3 minor joint bleeds per year 2: 1-2 major or 4-6 minor joint bleeds per year 3: ≥3 major or ≥7 minor joint bleeds per year MINOR JOINT BLEED: mild pain, minimal swelling, minimal restriction of motion, resolves within 24 hours of treatment MAJOR JOINT BLEED: pain, effusion, limitation of motion, failure to respond within 24 hours of treatment
Physical Exam	Swelling: None: 0 Present: 2 "S" is added to after score if chronic synovitis is present Muscle atrophy: None or minimal (<1 cm): 0 Present: 1 Axial deformity (measured only at knee or ankle): Knee 0= Normal = 0-7° valgus 1= 8-15° valgus or 0-5° varus 2= >15° valgus or >5° varus Ankle 0= No deformity 1= Up to 10° valgus or up to 5° varus 2= >10° valgus or >5° varus Crepitus on motion: None: 0 Present: 1 Range of motion (ROM): Loss of 10% of total full ROM: 0 Loss of 10-33 1/3% of total full ROM: 1 Loss of >33 1/3% of total full ROM: 2 Flexion contracture (measured only at hip, knee, or ankle): <15° fixed flexion contracture (FFC): 0 ≥15° FFC at hip or knee or equinus at ankle: 2 Instability: 0=None 1=Noted on examination but neither interferes with function nor requires bracing, 2=Instability that creates a functional deficit or requires bracing

Table 5
Gilbert Scale for Musculoskeletal Evaluation of Haemophilic Joints

X-Ray	Osteoporosis: Absent: 0 Present: 1 Enlarged epiphysis: Absent: 0 Present: 1 Irregular subchondral surface: Absent: 0 Surface partially involved: 1 Surface totally involved: 2 Narrowing of joint space: Absent: 0 Present with joint space <1 mm: 1 Present with joint space >1 mm: 2 Subchondral cyst formation: Absent: 0 1 cyst: 1 >1 cyst: 2 Erosion at joint margins: Absent: 0 Present: 1 Gross incongruence of articulating bone ends: Absent: 0 Slight: 1 Pronounced: 2 Joint deformity (angulation and/or displacement between articulating bones): Absent: 0 Slight: 1 Pronounced: 2

Source: Gilbert, 1993 [42]

- The Haemophilia Joint Health Score (HJHS) [41] was developed by the International Prophylaxis Study Group (IPSG) as a new scoring system for musculoskeletal evaluation optimized for use in children with no or minimal joint disease. The HJHS is better suited for children aged 4 – 18 years and all patients on primary prophylaxis than the Gilbert score, which was found to be too insensitive to identify earliest signs of joint disease. The HJHS includes the following parameters: swelling, duration of swelling, muscle atrophy, joint pain, crepitus on motion, flexion loss, extension loss, strength and global gait. The HJHS measures joint health, in the domain of body structure and function (i.e. impairment), of the joints most commonly affected by bleeding in haemophilia: the knees, ankles, and elbows. It can be used when there is a need for orthopedic intervention, or as an outcome measure of physiotherapy interventions.

It is appropriate for monitoring joint change over time or assessing efficacy of treatment regimens in children receiving both prophylactic and on-demand therapy. The HJHS 2.1 provides a total score (higher score is worse; max=124), joint specific scores, and a global gait score. (Table 6). The HJHS total score, calculated from the Sum of Joint Totals and Global Gait Score will be collected during screening, intervals, and termination visits or whenever the treating physician deems it appropriate.

Table 6
Haemophilia Joint Health Score (HJHS) for assessing Joint Impairment

Swelling	0 = no swelling 1 = mild 2 = moderate 3 = severe
Duration (swelling)	0 = no swelling or < 6 months 1 = ≥6 months
Muscle Atrophy	0 = none 1= mild 2 = severe
Joint Pain	0 = no pain through active range of motion 1 = no pain through active range, only pain on gentle overpressure or palpation 2 = pain through active range
Crepitus on Motion	0 = none 1= mild 2 = severe
Flexion Loss	0 = < 5° 1= 5° - 10° 2 = 11° - 20° 3 = > 20°
Extension Loss (from hyperextension)	0 = < 5° 1= 5° - 10° 2 = 11° - 20° 3 = > 20°

Table 6 **Haemophilia Joint Health Score (HJHS) for assessing Joint Impairment**	
Strength (using the Daniels & Worthingham's scale)	Within available ROM 0 = holds test position against gravity with maximum resistance (gr.5) 1 = holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4) 2 = holds test position with minimal resistance (gr.3+), or holds test position against gravity (gr. 3) 3 = able to partially complete ROM against gravity (gr.3-/2+), or through partial ROM gravity eliminated (gr.2-) 4 = Trace (gr.1) or no muscle contraction (gr.0) NE = non-evaluable
Global Gait (walking, stairs, running, hopping on 1 leg)	0 = all skills are within normal limits 1 = one skill is not within normal limits 2 = two skills are not within normal limits 3 = three skills are not within normal limits 4 = four skills are not within normal limits NE = non-evaluable

Source: Feldman et al, 2008 [41], HJHS Summary Score Sheet at http://www1.wfh.org/docs/en/Publications/Assessment_Tools/HJHS_Summary_Score.pdf

- X-ray using Pettersson scale (if available)
  - The World Federation of Hemophilia endorsed a radiographic scale, commonly referred to as the Pettersson scale [43], to measure hemophilia joint health status. Eight parameters are weighted and summed to give a score for the joint as shown in. Pettersson scores of all joints will be collected during screening, intervals, and termination visits or whenever the treating physician deems it appropriate.

Table 7
Pettersson Scale for Radiographic Evaluation of Hemophilic Joints

X-Ray	Osteoporosis: Absent: 0 Present: 1 Enlarged epiphysis: Absent: 0 Present: 1 Irregular subchondral surface: Absent: 0 Surface partially involved: 1 Surface totally involved: 2 Narrowing of joint space: Absent: 0 Present with joint space <1 mm: 1 Present with joint space >1 mm: 2 Subchondral cyst formation: Absent: 0 1 cyst: 1 >1 cyst: 2 Erosion at joint margins: Absent: 0 Present: 1 Gross incongruence of articulating bone ends: Absent: 0 Slight: 1 Pronounced: 2 Joint deformity (angulation and/or displacement between articulating bones): Absent: 0 Slight: 1 Pronounced: 2

Source: Pettersson H et al 1980 [43]

- Magnetic Resonance Imaging scoring system and or ultrasound scanning (if available and used at site)
  - Several MRI scoring systems have been developed to measure hemophilia joint health status. One of the most commonly used systems was one that was developed in Lund, Sweden.[44] MRI scores of all joints will be collected during screening, intervals, and termination visits or whenever the treating physician deems it appropriate. The scoring system [45,46,47] used shall be determined by the subject's radiologist.

- Ultrasound evaluation of joint status is currently being studied by international groups.[48] Ultrasound can be used to identify haemarthroses and to evaluate the synovium for signs of inflammation. Inflamed synovium demonstrates increased flow with colour and power Doppler imaging and it may be seen to be thickened and nodular. Ultrasound can distinguish between haemarthrosis and synovial hypertrophy. It has the ability of differentiating synovium hypertrophy and hemosiderin deposition.[49] Ultrasound analysis of joints will be collected during screening, annual intervals, and termination visits or whenever the treating physician deems it appropriate.

Table 8
Magnetic Resonance Imaging Scoring System Developed in Lund, Sweden

A Component	Subchondral Cyst
	Present in at least 1 bone
	Present in at least 2 bones
	>3 cysts in at least 1 bone
	>3 cysts in at least 2 bones
	Largest size >4 mm in at least 1 bone
	Largest size >4 mm in at least 2 bones
	Irregularity/erosion of subchondral cortex
	Present in at least 1 bone
	Present in at least 2 bones
	Involve more than half of joint surface in at least 1 bone
	Involve more than half of joint surface in at least 2 bones
	Chondral destruction
	Present in at least 1 bone
	Present in at least 2 bones
	Full thickness defect in at least 1 bone
	Full thickness defect in at least 2 bones
	Full thickness defect involves >1/3 of joint surface in at least 1 bone
	Full thickness defect involves >1/3 of joint surface in at least 2 bones
Effusion/hemarthrosis (e)	0 absent
Hypertrophic synovial (s)	1 equivocal
Hemosiderin (h)	2 small
	3 moderate
	4 large

Source: Lundin B et al. 2004 [44]

- Number of total target joints (defined as 3 or more bleeds in the same joint in a 6 month period [7])
- Number of invasive surgical procedures, such as (but not exclusively orthopedic) surgery, radiosynovectomy, and chemosynovectomy per year per patient

9.3.2 Quality of Life Variables

9.3.2.1 Health-Related Quality of Life

QoL questionnaires will be provided at the screening visit and on an annual basis to subjects or subjects' legally authorized representatives who opt to voluntarily complete them. Some QoL questionnaires may not be available in all languages and therefore will not be available at all study sites.

- SF-12v2, and EQ-5D questionnaires – for adult subjects ≥ 18 years
  - The SF-12v2 measures generic health-related quality of life.
  - The EQ-5D measures health utility and it is a descriptive system of health-related quality of life consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels of severity: no problems, some problems, extreme problems.
- SF-10, measures generic health-related quality of life for children aged 4-13 and is parent-completed.
- EQ-5D-Y (Youth version). Descriptive system of youth health-related quality of life states consisting of five dimensions (mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad or unhappy) each of which can take one of three responses. The responses record three levels of severity (no problems/some problems or a bit/a lot (of) problems or very) within a particular EQ-5D dimension. It can be parent-completed and used in children of age 7-17 [50,51,52]
- HemoQoL[iii] scale for both adults (Hem-A-QoL ≥ 18 years) and children (HemoQol) aged 4-17. The Haemo-QoL is a quality of life assessment instrument for children and adolescents with haemophilia. There are 3 sets of psychometrically tested questionnaire versions for three age groups of children as well as their parents. In addition to the full version, a short version for small children (4-7 years) containing 16 items and a short version for older children (8-16 years) containing 35 items were developed. An 8-item index version was developed spanning all age groups which is also available as a self and parent-report.

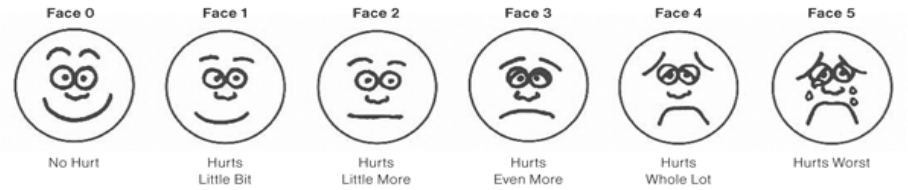
[iii] http://www.haemoqol.de

9.3.2.2 Pain

- Chronic pain (defined as "Continuous and/or intermittent pain, related to the pathophysiology of haemophilia, requiring intervention (pharmacological or non-pharmacological pain treatment), in which the cause of pain cannot be readily removed, occurring more than once a week and lasting 3 months or more") [1] associated with hemophilia
- Acute pain associated with bleeding episodes in haemophilia patients

  Chronic pain and acute pain associated with haemophilia will be assessed by

  - Numeric Rating Scale
    The numeric rating scale (NRS) is a unidimensional measure of pain intensity in adults. The most commonly iteration used is the 11-items NRS. The common format is a horizontal bar or line. Similar to the pain visual analogue scale (VAS), the NRS is anchored by describing pain severity extremes. It can be administered either verbally or graphically for self-completion and the subject is asked to indicate the numeric value on the segmented scale that best describes pain intensity.
  - Pediatric subjects or subjects that have difficulty quantifying their pain numerically can be asked to assess the pain by using the following Wong Baker Face Scale



Explain to the individual that each face is for an individual who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he does not hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although the individual does not have to be crying to feel this bad. Ask the individual to choose the face that best describes how he is feeling. This rating scale is recommended for individuals 3 years and older. Brief instructions: point to each face using the words to describe the pain intensity. Ask the individual to choose the face that best describes the pain and record the appropriate number.

During the screening and on an annual basis – or more frequently based on current standard at the site - the investigators shall ask subjects to rate the average level of chronic pain associated with haemophilia over the period of 4 weeks prior to visit date using the NRS. The scores will be recorded in subject diary and the completion of the NRS will be done on a voluntary basis.

During the interval and termination visits, the investigator will determine the level of completeness in record keeping. If the investigator decides not to transcribe the data into the CRF, a comment explaining the reason needs to be provided in the corresponding section of the CRF.

9.3.2.3 Daily Activity Level

Daily activity level, if available, will be assessed by Haemophilia Activity Level scale (HAL) [2,3] in adults and Pediatric Haemophilia Activity Level scale (PedHAL) in children.

- The HAL measures activities involving the upper extremities, basic activities involving the lower extremities and complex activities involving the lower extremities as well as an overall physical activity score for adults.. The aim of this questionnaire is to determine the ability of the subject to perform the following activities.
  - Lying down/ sitting / kneeling / standing
  - Functions of the legs
  - Functions of the arms
  - Use of transportation
  - Self-care
  - Household tasks
  - Leisure activities and sports
  - Adaptations and using an aid

  There are six different response options (Impossible, always, mostly, sometimes, rarely, never).
- The pedHAL measures a number of activities involving the upper extremities, basic activities involving the lower extremities and complex activities involving the lower extremities as well as an overall physical activity score for children. The aim of this questionnaire is to determine the ability of children to perform the following activities:-
  - Sitting / kneeling / standing
  - Legs
  - Arms
  - Use of transportation
  - Self-care
  - Household tasks
  - Leisure activities and sports
  - Adaptations and using an aid

9.3.3 Economic Variables

- Health resource use:
  - Number of visits at the site
  - Unscheduled visits at the site
  - Number of hospitalizations and length of stay (number of days) related to haemophilia (surgery excluded)
  - Length of stay in hospital per inpatient hospitalization
  - Number of days lost from school or work due to bleeding episodes
  - Antiphlogistic drug use

9.3.4 Pharmacodynamic Variables

- Individual pharmacodynamic properties (PD) of FEIBA NF by thrombin generation assay (TGA), if available

  TGA measures the thrombin concentrations before and after clot formation and it is very sensitive to variations in individual or groups of coagulation factors. *In vitro* spiking of high-titre inhibitor plasma with increasing concentrations of FEIBA NF resulted in the dose-dependent restoration of the thrombin-generating capacity of the FVIII-inhibitor plasma. It has been reported [53] that defective thrombin generation is reversed in patients with FVIII inhibitors within 30 min after a single injection of therapeutic doses of FEIBA NF. The changes in the kinetics of thrombin generation measured before, during and after FVIII-bypassing therapy reflect the pharmacological effect of the drug. TGA may enable the pharmacodynamic and pharmacokinetic properties of bypassing therapies to be monitored, thus helping to optimize treatment, however, more data on clinical efficacy in relation with TGA are needed [54]

  - Thrombin generation (TG) can be used to individualize FEIBA NF treatment as a component of overall coagulation monitoring for major surgeries [55,56,57]
  - Assessments from TGA [peak thrombin (nmol/L), ETP (area under the curve), lag time (time to start of observable thrombin generation), velocity index (nmol/L*min) and time to thrombin generation peak (min)] will be summarized for subjects with available data. Time points of blood collection and the method used for TGA execution will be collected and analysed. Date/time of the last FEIBA infusion, total units given (U), body weight (kg) at time of infusion, pre and post-infusion blood draws), the laboratory where TGA was assessed, and reason of infusion (i.e., to assess TGA) will be recorded

- The association between these parameters and bleeding rates, bleeding treatment efficacy and overall effectiveness, total dose (U/kg), and the total number of infusions for bleeding will be evaluated (treatment will be evaluated using a non-parametric Spearman's correlation coefficient, for both prophylaxis and on-demand treatment).

9.3.5 Safety Variables

Safety of FEIBA NF assessed by using the following endpoints (see also Section 11):

- Incidence, severity and relatedness of SAEs
- Incidence, severity and relatedness of NSAEs
- Incidence, severity and relatedness of thromboembolic events and thrombotic microangiopathy
- Incidence in safety profile of FEIBA used on-demand and prophylactically based on assessment of all SAEs in the respective sub-group

9.3.5.1 Medical History, Medications and Non-Drug Therapies

At screening, the subject's medical history, including haemophilia and treatment history, will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 11.2.4) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

9.3.5.2 Physical Examination

Physical examination will be performed according to local routine at annual visits to the site. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At subsequent study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 11.2.6) not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

9.3.5.3 Clinical Laboratory Parameters

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 11.1 , and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a preexisting disease (described in Section 11.2.6), or was due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie. because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. However, additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

9.3.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, adverse event (eg, death), discontinuation by subject [eg, lost to follow-up (defined as 3 documented unsuccessful attempts to contact the subject), dropout], physician decision (eg, progressive disease, non-compliance with medicinal product/protocol violation(s), recovery, disappearance of the inhibitor, success of the ITI treatment), study terminated by responsible party, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

The reason for discontinuation will be recorded on the CRF, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations performed as part of the evaluation of the event will take place under the direction of the investigator and will be reported to the sponsor . Details of the outcome may be reported to the appropriate regulatory authorities by the responsible party.

9.4 Data Sources

9.4.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, imaging-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

9.4.2 Subject Diary

It is considered standard practice for subjects with hemophilia to maintain a diary which captures treatments and disease related data. A subject diary will be provided to each subject at the screening visit and at annual interval visit(s), as needed, to help with the standardization of data collection method. Nevertheless, the completion of the diary is a voluntary effort by the individual subject or subject's legally authorized representative. A subject diary should allow to capture the following information:

- Infusion log for FEIBA NF
- Bleeding episodes
- Effectiveness assessment for treatment of each bleed
- Effectiveness assessment for prophylaxis therapy
- Acute pain associated with hemophilia, as measured with individual bleeding episodes, using the NRS (or Wong Baker Face Scale). VAS can also be used if routine practice at the centre. Acute pain will be assessed by the subject for each bleeding event and reported on the diary
- Chronic pain will be assessed using NRS on annual basis or more frequently according to routine practice at the site.
- Number of days lost from school or work due to bleeding episodes or their treatment
- Adverse events
- Concomitant medications / Non-drug therapies
- Duration of infusion of FEIBA NF

Diary data will be captured remotely by the subject entering them into a particular part of the electronic CRF (e-CRF). During the study, the investigator has access to the database holding the subject diary data. Upon retrieval of subject diaries at site closure, the site will receive the pdf files with the subject entries, including the audit trail.

All AEs regardless of causality and the number of bleed occurrences recorded in the subject diary during study participation period will be transcribed onto the CRF. For other types of data, such as global effectiveness and pain assessments, in the subject diary, every attempt will be made to collect all data as stated in this protocol. There will be no imputation on any endpoint in this study. Therefore, missing data will be labeled as such.

9.5 Study Size

As no hypothesis testing or interval estimation will be applied, the sample size for the study is not based on statistical considerations. The sample size of approximately 55 evaluable subjects was selected as a reasonable number for a non-interventional study to recruit in the two-year enrolment period planned for the study.

9.6 Data Management

9.6.1 Data Collection Methods

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), subject diaries (if used), and data clarifications requested by the responsible party.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs (e-CRFs) are provided by the responsible party, only authorized study site personnel will record or change data on the CRFs. All data should preferably be entered on the CRFs during the study visit. If this is not possible due to time restrictions, the data will be recorded on paper; this documentation will be considered source documentation. Changes to an e-CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of e-CRFs for each subject will remain in the investigator file at the study site.

The handling of data by the responsible party, including data quality assurance, will comply with regulatory guidelines and the standard operating procedures of the responsible party. Data management and control processes specific to the study will be described in the data management plan (see Section 14.1).

9.6.2 Software

All data processing, summarization and analyses will be performed with the SAS®, version 9.1.3 software or higher.

9.7 Data Analysis

9.7.1 Datasets and Analysis

The Safety Analysis Set (SAS) will consist of data for all subjects who were enrolled, met all inclusion and exclusion criteria, and received at least 1 infusion of FEIBA NF.

9.7.1.1 Calculation of Annualized Bleeding Rates (ABR)

The annualized bleeding rates (ABR) will be calculated as follows: (total number of bleeding episodes÷observed treatment period in days) * 365.25.

The treatment period for emergency surgery will be excluded from the bleed rate calculation.

Bleeding occurring prior to the first prophylactic infusion will not be included for the estimation of bleed rate. The observation period for the on-demand regimen will commence on the day of enrollment (met all inclusion and exclusion criteria); the period for the prophylaxis arm will commence at the first prophylactic infusion once enrolled (met all inclusion and exclusion criteria).

9.7.1.2 Minimal Observed Treatment Period to Estimate ABR

For enrolled subjects that have met all inclusion and exclusion criteria, subjects who have at least 1 assessment [defined as having a minimum of 3-month (≥90 days) observational period on regimen] but do not complete the full study period of four years, the annualized bleeding rate will be estimated from the interval assessments.

9.7.2 Handling of Missing, Unused, and Spurious Data

If a subject's weight is missing from any infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose (U/kg).

In general, no additional techniques will be employed to adjust for missing data.

9.7.3 Methods of Analysis

Descriptive statistics of all endpoints will include specifically but not exclusively, arithmetic mean, standard deviations, medians, minimum, maximum, 25th and 75th percentiles, proportions, frequency counts, and 95% confidence intervals of select point estimates. Figures will be prepared to illustrate the patterns of data over time where appropriate. The number of subjects included in the analysis set will be reported.

9.7.3.1 Primary Endpoint

The primary endpoint, the ABR of all types of bleeding episodes, will be calculated for each subject and described for each regimen (on-demand and prophylaxis).

Separate descriptive efficacy analyses of ABR will be provided for each of the following treatment regimens, assuming minimum observed period is satisfied (≥90 days):

- On-demand treatment
- Standard prophylaxis
  - continuous prophylaxis (≥46 weeks: long-term) [6]
  - intermittent prophylaxis (≥12 weeks-46 weeks)
  - episodic prophylaxis (<12 weeks)
  - peri-ITI prophylaxis
- TGA-guided dosing for prophylaxis treatment
- TGA-guided dosing for on-demand treatment

9.7.3.2 Methods of Analysis for Other Primary Efficacy Criteria

The annualized rate of bleeding episodes in joints, target joints, and other anatomical locations for on-demand and prophylaxis subjects will be summarized.

The frequency distribution for number of infusions for bleed treatment will be reported for each of the treatment regimens. The median number of infusions per bleeding episode for each subject will be calculated. The weight-adjusted dose (U/kg) per bleeding episode per subject will be described for on-demand and prophylaxis treatment regimens.

For treatment of bleeding episodes:

Corresponding to all treated (with FEIBA NF) bleeding episodes the following parameters and statistics will be computed separately by each treatment regimen (prophylaxis, on-demand):

Parameter	Statistics
Total number of subjects infused	Sum
Total exposure days	Median(Q1,Q3)
Total number of infusions	Median(Q1,Q3)
Number of unique lots used	Sum
Units administered per subject, per infusion (U)	Median(Q1,Q3)
Units administered per subject, per week (U)	Median(Q1,Q3)
Units administered per subject, per month (U)	Median(Q1,Q3)
Annualized units administered, per subject (U)	Median(Q1,Q3)
Total units administered, per subject (U)	Median(Q1,Q3)
Weight-adjusted dose per subject, per infusion (U/kg)	Median(Q1,Q3)
Weight-adjusted dose per subject, per week (U/kg)	Median(Q1,Q3)
Weight-adjusted dose per subject, per month (U/kg)	Median(Q1,Q3)
Annualized weight-adjusted dose, per subject (U/kg)	Median(Q1,Q3)
Total weight-adjusted dose, per subject (U/kg)	Median(Q1,Q3)

Total number (%) of treated bleeds and their corresponding hemostatic efficacy ratings using an “excellent-to-poor” 4-point Likert scale by the subjects or caregiver for treatments given at home or by the investigator for treatments given in the hospital/clinic.

For prevention of bleeding episodes:

Corresponding to subjects given prophylaxis infusions or on demand regimen (FEIBA NF) in this study, the following parameters and statistics will be computed by treatment regimen (prophylaxis, on-demand):

Parameter	**Statistics**
Total number of subjects infused	Sum
Total exposure days	Median(Q1,Q3)
Total number of infusions	Median(Q1,Q3)
Number of unique lots used	Sum
Units administered per subject, per infusion (U)	Median(Q1,Q3)
Units administered per subject, per week (U)	Median(Q1,Q3)
Units administered per subject, per month (U)	Median(Q1,Q3)
Annualized units administered, per subject (U)	Median(Q1,Q3)
Total units administered, per subject (U)	Median(Q1,Q3)
Weight-adjusted dose per subject, per infusion (U/kg)	Median(Q1,Q3)
Weight-adjusted dose per subject, per week (U/kg)	Median(Q1,Q3)
Weight-adjusted dose per subject, per month (U/kg)	Median(Q1,Q3)
Annualized weight-adjusted dose, per subject (U/kg)	Median(Q1,Q3)
Total weight-adjusted dose, per subject (U/kg)	Median(Q1,Q3)

Efficacy will be assessed by a "excellent-to-poor" 4-point Likert scale by the subjects or care-giver at the end of each prophylaxis period (possibly rated within 24 hours from the end of the prophylactic treatment) or on an annual basis depending on which occurs first. The occurrence of new target joints and bleeding episodes used to detect new target joints will be summarized by treatment regimen

9.7.3.3 Secondary Endpoints

The methods of analysis for the secondary efficacy endpoints (see Section 9.1.2.1) are, if available:

- Physical exam using only the pain, bleeding, and physical exam parameters of the Gilbert scale will be summarized for timepoints 0 (screening visit), 1, 2, 3, and 4 (termination visit) years after study start.
- MRI scoring will be summarized for timepoints 0 (baseline), 1, 2, 3 and 4 years after study start (if available).

- X-ray by Pettersson score will be summarized for timepoints 0, 1, 2, 3 and 4 years after study start (if available).
- HJHS will be summarized for timepoints 0, 1, 2, 3 and 4 years after study start (if available).
- Number of invasive surgical procedures, such as (but not exclusively orthopedic) surgery, radiosynovectomy, and chemosynovectomy per year per subject

9.7.3.4 Methods of Analysis for Safety Endpoints

The analysis of AEs will be descriptive. All AEs will be categorized according to MedDRA dictionary and summarized by system organ class and preferred term. AEs for which the investigator does not state the relationship to FEIBA NF administration will be included. All AEs will be cross-tabulated for relatedness, seriousness, and severity.

9.7.3.5 Methods of Analysis for Health Related Quality of Life (HRQoL) Endpoints

HRQoL assessments, chronic pain scales, daily activity level will be summarized by treatment regimen (on-demand, prophylaxis). If available, changes from baseline to follow-up study visit will be summarized by treatment regimen. Below is list of HRQoL assessment, if available:

- SF-12v2, and EQ-5D questionnaires – for adult subjects
  - The SF-12v2 measures generic health-related quality of life for adults.
  - The EQ-5D measures health utility in adult subjects.
- SF-10, and EQ-5D-Y questionnaires – for pediatric subjects
  - The SF-10 measures generic health-related quality of life for children aged 4-13 years and is parent-completed.
  - EQ-5D-Y (Youth version). Descriptive system of youth HRQoL states consisting of five dimensions in subjects aged 7-17 years and can be parent-completed
- Chronic pain associated with hemophilia, defined as “Continuous and/or intermittent pain, related to the pathophysiology of haemophilia, requiring intervention (pharmacological or non-pharmacological pain treatment), in which the cause of pain cannot be readily removed, occurring more than once a week and lasting 3 months or more”) [41] and acute pain associated with bleeding episodes will be assessed by

- Numeric Rating Scale (NRS): the NRS measures pain intensity in adults. The most commonly iteration used is the 11-item NRS and its common format is a horizontal bar or line and it is anchored by describing pain severity extremes.
- Wong Baker Face Scale in pediatric subjects

- Daily activity level will be assessed by
  - Haemophilia Activity Level scale (HAL) in adults
  - Pediatric Haemophilia Activity Level scale (PedHAL) in children aged 8-17 years

9.7.3.6 Methods of Analysis for Health Resource Used Related (HRUR) Endpoints

All HRUR parameters will be summarized by treatment regimen (on-demand, prophylaxis). If available, changes from baseline to each follow-up study visit will summarized by treatment regimen. Below is list of all HRUR parameters:

- Health resource use: number of visits at the site
- Unscheduled visits at the site
- Number of hospitalizations related to haemophilia (surgery excluded)
- Length of stay in hospital per stay
- Antiphlogistic drug use
- Infusion log for FEIBA NF
- Acute pain associated with haemophilia, as measured with individual bleeding episodes, using the NRS or the Wong Baker Face Scale in pediatric subjects
- Chronic pain will be assessed on annual basis or more frequently based on current standard at the centre at the screening visit, on each annual visit and at the termination visit by using the NRS or the Wong Baker Face Scale in pediatric subjects
- Number of days lost from school or work due to bleeding episodes or their treatment
- Concomitant medications /Non-drug therapies
- Duration of infusion of FEIBA NF (reconstitution time excluded)

9.7.3.7 Methods of Analysis Pharmacodynamic (TGA) Endpoints

Descriptive statistics and figures will be computed by treatment regimen (on-demand, prophylaxis) to assess the pharmacodynamic responses from TGA parameters over the course of the study. Means (SD), medians (IQR), first quartile, third quartile, 95% confidence intervals of point estimates, maximum, and/or minimum will be generated. There will be no formal statistical comparison conducted. TGA parameters will include peak thrombin [nmol/l], endogenous thrombin potential (ETP, area under the curve) [nmol*min/L], onset time (time to the start of observable thrombin generation) [minutes], and peak time (time to reach the peak thrombin) [minutes].

The association between TGA parameters and bleed rates, total dose (U/kg), and the number of infusions for bleeding treatment will be evaluated using a non-parametric Spearman's correlation coefficient by independent treatment regimens (on-demand and prophylaxis).

9.7.3.8 Planned Interim Analysis of the Study

Only subjects that were enrolled and met all inclusion/exclusion criteria will be included in interim analyses.

The first study interim analysis is planned after all subjects are enrolled. All the following 3 interim study analyses will be available in May on annual basis in the period 2019-2021 Regular safety updates and study progress reports are to be scheduled.

9.8 Quality Control

9.8.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the competent/health authority and/or EC, as applicable), ICH GCP and applicable regulatory requirements as described in the Non-interventional Trial Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the responsible party. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

9.8.2 Direct Access to Source Data/Documents

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the responsible party or its representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Non-interventional Trial Agreement. If contacted by an applicable regulatory authority, the investigator will notify the responsible party of contact, cooperate with the authority, provide the responsible party with copies of all documents received from the authority, and allow the responsible party to comment on any responses, as described in the Non-interventional Trial Agreement.

9.8.3 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the responsible party.

9.8.4 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Non-interventional Trial Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan (see Section 14.1).

9.8.5 Auditing

The responsible party and/or responsible party's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP. and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Non-interventional Trial Agreement. Auditing processes specific to the study will be described in the auditing plan (see Section 14.1).

9.8.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the responsible party immediately by phone and confirm notification to the responsible party in writing as soon as possible, but within 1 calendar day after the change is implemented. The responsible party (Baxalta) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the responsible party may terminate the investigator's participation. The responsible party will notify the EC and applicable regulatory authorities of any investigator termination.

9.9 Limitations of the Research Methods

This prospective, uncontrolled, observational, open-label, non-interventional multicenter cohort study will provide a real-life picture on the use of FEIBA NF in patients with congenital haemophilia A or B and inhibitors. Due to the non-interventional nature of the study, the amount of data that becomes available to be entered by the investigator or designee is beyond the responsible party´s control.

9.10 Other Aspects

This section is not applicable, as all aspects of the research method are covered by the previous sections

10. PROTECTION OF HUMAN SUBJECTS

10.1 Compliance Statement

This study will be conducted in accordance with this protocol and applicable national and local requirements for good pharmacovigilance practices.

10.2 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Non-interventional Trial Agreement.

10.3 Ethics Committee(s) and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the responsible party's receipt of approval/favorable opinion from the EC and, if required, upon the responsible party's notification of applicable regulatory authority(ies) approval, as described in the Non-interventional Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and relevant regulatory authorities, where applicable. The protocol amendment will only be implemented upon the responsible party's receipt of approval and, if required, upon the responsible party's notification of applicable regulatory authority(ies) approval.

10.4 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements. An assent form may be provided and should be signed by patients less than 18 years of age. Before use, the informed consent form will be reviewed by the responsible parties and approved by the EC and regulatory authority(ies), where applicable, (see Section 10.3). The informed consent form will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by applicable regulatory requirements. Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study.

By signing the informed consent form, patients or their legally authorized representative(s) agree to participate in the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The responsible parties will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with medicinal product exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consent to participate in the study (see Section 9.2.4).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Assessment of Adverse Events

Each AE from the point of enrolment until study completion will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definitions in Section 11.2). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.2.2 and Section 11.2.3
- Severity as defined in Section 11.2.4
- Causal relationship to medicinal product exposure as defined in Section 11.2.5

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness.

11.2 Definitions

11.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered medicinal product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of a medicinal product, whether or not considered causally related to the medicinal product. Non serious bleeding events due to the underlying disease are not considered AE and inhibitors of any titer are not to be considered an AE. Anamnestic response to FEIBA NF (the rise of pre-existing inhibitor titer following the administration of FEIBA NF) is considered an AE. Events that do not necessarily meet the definition of AEs, regardless of causal association with medicinal product, should be treated as AEs because they may be reportable to Regulatory Authorities according to AE reporting regulation; these include the following:

1. Medicinal product overdose, whether accidental or intentional
2. Medicinal product abuse
3. An event occurring from medicinal product withdrawal
4. Any failure of expected pharmacological action
5. Unexpected therapeutic or clinical benefit from FEIBA NF
6. Medication errors (i.e. incorrect route of administration, incorrect dosage, use of incorrect product)

11.2.2 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
  - Thromboembolic events (e.g., Myocardial infarction, Stroke, TIA, DVT, PE, DIC)
  - Thrombotic microangiopathy

11.2.3 Non-Serious Adverse Event

A non-serious Adverse Event (NSAEs) is an AE that does not meet the criteria of an SAE.

11.2.4 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequel.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequel, which require (prolonged) therapeutic intervention.

11.2.5 Causality

Causality is a determination of whether there is a reasonable possibility that the medicinal product is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE assessed as not related or unlikely related, the investigator shall provide an alternative etiology. For each AE, the investigator will assess the causal relationship between the medicinal product and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the medicinal product (ie, does not follow a reasonable temporal relationship to the administration of medicinal product or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the medicinal product
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of medicinal product
  - An alternative etiology is equally or less likely compared to the potential relationship to the medicinal product
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of medicinal product, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the medicinal product as evidenced by measurement of the medicinal product concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

11.2.6 Preexisting Diseases

Preexisting diseases that are present before entry in to the study are described in the medical history; those that manifest with the same severity, frequency, or duration after medicinal product exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF. Non serious bleeding events will not be considered as an AE if due to the underlying disease.

11.2.7 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, product labeling). "Unexpected" also refers to the AEs that are mentioned in the product labeling as occurring with a class of medicinal products or as anticipated from the pharmacological properties of the medicinal product, but are not specifically mentioned as occurring with the particular medicinal product under investigation.

For the purposes of this study, each unexpected AE experienced by a subject undergoing on-demand or prophylaxis therapy or ITI with FEIBA NF will be recorded on the AE CRF.

11.2.8 Untoward Medical Occurrences Not Considered Adverse Events

For the purposes of this study, each of the following events experienced after the Informed Consent signature will not be considered an AE, and thus, not included in the analysis of AEs:

- Non serious bleeding events that are considered due to the underlying disease by the investigator.
- Elective surgeries: Elective and planned surgeries, when these surgeries relate to a preexisting disease (see also Section 11.2.6) that has not worsened during study participation, will not be considered as (S)AEs

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The investigator will comply with the publication policy as described in the Non-interventional Trial Agreement.

13. REFERENCES

1. Holstein K, Klamroth R, Richards M, Carvalho M, Pérez-Garrido R, Gringeri A. Pain management in patients with haemophilia: a European survey. *Haemophilia*. 2012;18(5):7443-7452.

2. van Genderen FR, van Meeteren NLU, van der Bom JG, et al. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. *Haemophilia*. 2004;10(5):565-571.

3. van Genderen FR, Westers P, Heijnen L, et al. Measuring patients' perceptions on their functional abilities: Validation of the Haemophilia Activities List. *Haemophilia*. 2006;12(1):36-46.

4. Key NS. Inhibitors in congenital coagulation disorders. *Br J Haematol*. 2004;127(4):379-391.

5. White GC, II, Rosendaal F, Aledort LM, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost*. 2001;85(3):560-575.

6. Berntorp E, Astermark J, Björkman S, et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia*. 2003;9 Suppl 1:1-4.

7. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N Engl J Med*. 2011;365(18):1684-1692.

8. Soucie JM, Evatt B, Jackson D, Investigators HSSP. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. *Am J Hematol*. 1998;59(4):288-294.

9. Leissinger CA. Prophylaxis in haemophilia patients with inhibitors. *Haemophilia*. 2006;12 Suppl 6:67-72; discussion 72-73.

10. Santagostino E, Mancuso ME, Rocino A, et al. Environmental risk factors for inhibitor development in children with haemophilia A: A case-control study. *Br J Haematol*. 2005;130(3):422-427.

11. Oldenburg J, Pavlova A. Genetic risk factors for inhibitors to factors VIII and IX. *Haemophilia*. 2006;12 Suppl 6:15-22.

12. Gouw SC, van der Bom JG, van den Berg HM. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: The CANAL cohort study. *Blood*. 2007;109(11):4648-4654.

13. Turecek PL, Varadi K, Gritsch H, et al. Factor Xa and prothrombin: mechanism of action of FEIBA. *Vox Sang*. 1999;77 Suppl 1:72-79.

14. Scalone L, Mantovani LG, Mannucci PM, Gringeri A, Investigators CS. Quality of life is associated to the orthopaedic status in haemophilic patients with inhibitors. *Haemophilia*. 2006;12(2):154-162.

15. Antunes SV, Vicari P, Cavalheiro S, Bordin JO. Intracranial haemorrhage among a population of haemophilic patients in Brazil. *Haemophilia*. 2003;9(5):573-577.

16. Valentino LA, Martinowitz U, Doolas A, Murali P. Surgical excision of a giant pelvic pseudotumour in a patient with haemophilia A. *Haemophilia*. 2006;12(5):541-544.

17. Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients--a long-term follow-up. *J Intern Med*. 1997;241(5):395-400.

18. Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med*. 1994;236(4):391-399.

19. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357(6):535-544.

20. DiMichele D, Negrier C. A retrospective postlicensure survey of FEIBA efficacy and safety. *Haemophilia*. 2006;12(4):352-362.

21. Hilgartner MW, Makipernaa A, DiMichele DM. Long-term FEIBA prophylaxis does not prevent progression of existing joint disease. *Haemophilia*. 2003;9(3):261-268.

22. Valentino LA. FEIBA prophylaxis for patients with haemophilia and inhibitors. *Haemophilia*. 2006;12 Suppl 5:26-31.

23. Leissinger CA, Becton DL, Ewing NP, Valentino LA. Prophylactic treatment with activated prothrombin complex concentrate (FEIBA©) reduces the frequency of bleeding episodes in paediatric patients with haemophilia A and inhibitors. *Haemophilia*. 2007;13(3):249-255.

24. Ewing NP, Pullens L, De Guzman C. Anamnesis in patients with Hemophilia and Inhibitors who receive activated Prothrombin Complex Concentrates for prophylaxis. *J Thromb Haemost*. 2007;5 Suppl 2.

25. Lambert T, Fressinaud E, Goudemand J, Rafowicz A. Can long-term prophylaxis with APCC improve the bleeding rate and quality of life of frequently bleeding haemophiliacs with inhibitors? *Haemophilia*. 2006;12 Suppl 2:63.

26. Valentino L. Efficacy and safety of FEIBA VH prophylaxis in a patient with hemophilia B and a high-titer inhibitor. *J Thromb Haemost*. 2005;3 Suppl 1.

27. Hoots WK, Ebbesen LS, Konkle BA, et al. Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors. *Haemophilia*. 2008;14(3):466-475.

28. Ekert H, Brewin T, Boey W, Davey P, Tilden D. Cost-utility analysis of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX. *Haemophilia*. 2001;7(3):279-285.

29. Gringeri A, Mantovani LG, Scalone L, Mannucci PM, Group CS. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. *Blood*. 2003;102(7):2358-2363.

30. Gringeri A, Leissinger C, Cortesi PA, et al. Health-related quality of life in patients with haemophilia and inhibitors on prophylaxis with anti-inhibitor complex concentrate: results from the Pro-FEIBA study. *Haemophilia*. 2013;19(5):736-743.

31. Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia*. 2014;20(1):65-72.

32. Gringeri A, Lambert T, Street A, Aledort L, Group TAAPWGotIPS. Tertiary prophylaxis in adults: is there a rationale? *Haemophilia*. 2012;18(5):722-728.

33. Négrier C, Lienhart A, Numerof R, et al. SURgical interventions with FEIBA (SURF): International registry of surgery in haemophilia patients with inhibitory antibodies. *Haemophilia*. 2013;19(3):e143-e150.

34. Ehrlich HJ, Henzl MJ, Gomperts ED. Safety of factor VIII inhibitor bypass activity (FEIBA®): 10-year compilation of thrombotic adverse events. *Haemophilia*. 2002;8(2):83-90.

35. Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor vIII inhibitor bypass activity. *J Thromb Haemost*. 2004;2(10):1700-1708.

36. Hilgartner MW, Knatterud GL, Group FS. The use of factor eight inhibitor by-passing activity (FEIBA immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. *Blood*. 1983;61(1):36-40.

37. Hilgartner M, Aledort L, Andes A, Gill J. Efficacy and safety of vapor-heated anti-inhibitor coagulant complex in hemophilia patients. FEIBA Study Group. *Transfusion*. 1990;30(7):626-630.

38. Negrier C, Goudemand J, Sultan Y, Bertrand M, Rothschild C, Lauroua P. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. French FEIBA Study Group. Factor Eight Bypassing Activity. *Thromb Haemost*. 1997;77(6):1113-1119.

39. Glomstein A, Gronhaug S, Tjonnfjord G. Home treatment with FEIBA, the Norwegian experience:2002.

40. Perry D, Berntorp E, Tait C, et al. FEIBA prophylaxis in haemophilia patients a clinical update and treatment recommendations. *Haemophilia*. 2010;16(1):80-89.

41. Feldman BM, Funk SM, Bergstrom BM, et al. Validation of a new pediatric joint scoring system from the international hemophilia prophylaxis study group: Validity of the hemophilia joint health score (HJHS). *Arthritis Care Res*. 2011;63(2):223-230.

42. Gilbert MS. Prophylaxis: musculoskeletal evaluation. *Semin Hematol*. 1993;30(3 Suppl 2):3-6.

43. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res*. 1980(149):153-159.

44. Lundin B, Pettersson H, Ljung R. A new magnetic resonance imaging scoring method for assessment of haemophilic arthropathy. *Haemophilia*. 2004;10(4):383-389.

45. Lundin B, Ljung R, Pettersson H, (PEDNET) TEPNfHM. MRI scores of ankle joints in children with haemophilia - comparison with clinical data. *Haemophilia*. 2005;11(2):116-122.

46. Kilcoyne RF, Nuss R. Radiological assessment of haemophilic arthropathy with emphasis on MRI findings. *Haemophilia*. 2003;9 Suppl 1:57-63.

47. Nuss R, Kilcoyne RF, Geraghty S, et al. MRI findings in haemophilic joints treated with radiosynoviorthesis with development of an MRI scale of joint damage. *Haemophilia*. 2000;6(3):162-169.

48. de Moerloose P, Fischer K, Lambert T, et al. Recommendations for assessment, monitoring and follow-up of patients with haemophilia. *Haemophilia*. 2012;18(3):319-325.

49. Doria AS. State-of-the-art imaging techniques for the evaluation of haemophilic arthropathy: Present and future. *Haemophilia*. 2010;16 Suppl 5:107-114.

50. Jelsma J. A comparison of the performance of the EQ-5D and the EQ-5D-Y health-related quality of life instruments in South African children. *Int J Rehabil Res*. 2010;33(2):172-177.

51. Scalone L, Tomasetto C, Matteucci MC, et al. Assessing quality of life in children and adolescents: Development and validation of the Italian version of the EQ-5D-Y. *Ital J Public Health*. 2011;8(4):331-341.

52. Rabin R, Oemar M, Oppe M, Janssen B, Herdman M, Group E. EQ-5D-5L User guide: Basic information on how to use the EQ-5D-5L instrument, Version 4.0:2011:24. Web Link: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-3L.pdf

53. Varadi K, Turecek PL, Schwarz HP. Thrombin generation assay and other universal tests for monorting haemophilia therapy. *Haemophilia*. 2004;10 Suppl 2:17-21.

54. Varadi K, Negrier C, Berntorp E, et al. Monitoring the bioavailability of FEIBA with a thrombin generation assay. *J Thromb Haemost*. 2003;1(11):2374-2380.

55. Rangarajan S, Austin S, Goddard NJ, et al. Consensus recommendations for the use of FEIBA® in haemophilia A patients with inhibitors undergoing elective orthopaedic and non-orthopaedic surgery. *Haemophilia*. 2013;19(2):294-303.

56. Dargaud Y, Lienhart A, Meunier S, et al. Major surgery in a severe haemophilia A patient with high titre inhibitor: use of the thrombin generation test in the therapeutic decision. *Haemophilia*. 2005;11(5):552-558.

57. Dargaud Y, Lienhart A, Negrier C. Prospective assessment of thrombin generation test for dose monitoring of bypassing therapy in hemophilia patients with inhibitors undergoing elective surgery. *Blood*. 2010;116(25):5734-5737.

14. ANNEXES

14.1 List of Stand Alone Documents

No.	Document Reference No.	Date	Title
1	Study Team Roster_V35	**05 Oct 2017**	**Study Organization**
2	CMP V 2.0	21 Mar 2016	**Clinical Monitoring Plan**
3	DMP V 2.0	13 Oct 2015	**Data Management Plan**
4	Number	Not finalized	**Auditing Plan**

Study Organization: The name and contact information of the individuals involved with the study (eg, investigator(s), responsible party's medical expert and study monitor, responsible party's representative(s), laboratories, steering committees, and oversight committees [including ECs, as applicable] will be maintained by the responsible party and provided to the investigator.

14.2 ENCePP Checklist for Study Protocols

Refer to the completed ENCePP Checklist.

14.3 Additional Information

14.4 Summary of Changes

14.4.1 Protocol Amendment 2 Changes

In this section, changes from global Amendment 1 of the Protocol, dated 2015 MAR 25, are described and their rationale is given.

1. Section 1 Study Personnel
   Description of Change: Medical Expert was changed from [redacted] to [redacted]
   Purpose for Change: To reflect change in Medical Director of the study

2. Section 1 Study Personnel
   Description of Change: Authorized Representative (Signatory) name was changed from [redacted] to [redacted]
   Purpose for Change: To reflect change in Authorized Representative (Signatory) of the study

3. Section 1 Study Personnel
   Description of Change: MAH Contact Person was changed from [redacted] to [redacted]
   Purpose for Change: To reflect change in MAH Contact Person of the study

4. Section 3 Responsible Parties
   Description of Change: Autorized Representative (Signatory)/Reponsible Party was changed from [redacted] to [redacted]
   Purpose for Change: To reflect change in Autorized Representative (Signatory)/Reponsible Party

5. Section 4 Abstract
   Description of Change: In "Exclusion criterion" number four the word "interventional" was included
   Purpose for Change: To clarify "Exclusion criterion" number four

6. Section 4 Abstract
   Description of Change: previous milestones for Interim Study Reports have been replaced with new milestones
   Purpose for Change: To reflect updated estimation of Interim Study Reports

7. Section 6 Milestones
   Description of Change: previous milestones for Interim Study Reports have been replaced with new milestones
   Purpose for Change: To reflect updated estimation of Interim Study Reports

8. Throughout the document
   Description of Change: Planned number of subjects was changed from "approximately 100" to "approximately 55"
   Purpose for Change: To reflect updated estimation

9. Section 9 Research Methods
   Description of Change: in" Primary Endpoints" the second assessment was changed from "For prevention of bleeding episodes and in subject on on-demand treatment" to "For prevention of bleeding episode"
   Purpose for Change: To make it consistent with the description in other sections

10. Section 9 Research Methods
    Description of Change: In "Secondary Endpoints" the sixth assessment of Joint Health/Function Outcomes was changed from "Possible correlation between period of time on prophylaxis and other secondary efficacy criteria" to "Number of breakthrough bleeding events in patients on prophylaxis and number of consecutive months on prophylaxis"
    Purpose for Change: To align assessment with evaluation criteria

11. Section 9 Research Methods
    Description of Change: in "Health-Related Quality of Life and throughout the document" "Haem-A-QoL scale for adults (>18 years)", "HaemoQoL for children aged 4-17 years" and "Functional Independence Score in Haemophilia (FISH) in adults" were removed
    Purpose for Change: To align with EDC data entry

12. Section 9 Research Methods
    Description of Change: in "Other Secondary Objectives and throughout the document" "Physiotherapy" was removed
    Purpose for Change: To align with EDC data entry

13. Description of Change: In "Safety", at the end of the third endpoint,"and thrombotic microangiopathy" was added"
Purpose for Change: As per PRAC recommendations and few Regulatory Agencies request

14. Section 9 Research Methods
Description of Change: in "Safety" the fourth bullet point "Difference in safety profile of FEIBA used on-demand vs prophylactically based on assessment of all SAEs in the respective group" was changed to "Incidence in safety profile of FEIBA used on-demand and prophylactically based on assessment of all SAEs in the respective sub-group"
Purpose for Change: To align with evaluation criteria

15. Section 9 Research Methods
Description of Change: In "Duration of Study Period and Subject Participation", the duration of study was changed from 6 years to "approximately 7 years"
Purpose for Change: To reflect extension timeline of study duration

16. Section 9 Research Methods
Description of Change: In "Duration of Study Period and Subject Participation", Subject recruitment period was changed from 2 years to "approximately 3 years"
Purpose for Change: To reflect extension timeline of study recruitment period

17. Section 9 Research Methods
Description of Change: In "Variables", the analysis of "Haemostatic and Preventive Efficacy" (first bullet point) was changed from "For treatment of bleeding episodes in subjects on on-demand treatment" to "For treatment of bleeding episodes in subjects on on-demand treatment and for breakthrough bleeds in subjects on prophylaxis treatment"
Purpose for Change: To increase consistency with patient treatments

18. Section 9 Research Methods
Description of Change: In "Variables". the analysis of "Haemostatic and Preventive Efficacy" (second bullet point) the words "required to control bleed" were cancelled in all the three sub-points
Purpose for Change: To increase consistency of analysis

19. Description of Change: In "Variables", in the third endpoint of the "Safety Variables" (third bullet point) „"and thrombotic microangiopathy" was added"
Purpose for Change: As per PRAC recommendations and few Regulatory Agencies request

20. Section 9 Research Methods
Description of Change: In "Variables", the fourth endpoint of the "Safety Variables" (fourth bullet point) was changed from "Difference in safety profile of FEIBA used on-demand vs prophylactically based on assessment of all SAEs in the respective group" to "Incidence in safety profile of FEIBA used on-demand and prophylactically based on assessment of all SAEs in the respective sub-group"
Purpose for Change: To align with evaluation criteria

21. Section 9 Research Methods
Description of Change: In "Data Analysis", in the "Datasets and Analysis" the specifications of the "EFAS", "HRQoLAS", "PEAS", "PDAS", "JHFAS" were cancelled
Purpose for Change: To simplify analysis, prevent bias and align with new templates

22. Section 9 Research Methods
Description of Change: In "Data Analysis", in the "Primary Endpoint" the introductory sentence was changed from "Assuming treatment regimens are mutually exclusive (on-demand, prophylaxis), the following method of analysis will be applied to the efficacy endpoint. The primary endpoint, the ABR of all types of bleeding episodes, will be calculated for each subject and described for each regimen (on-demand and prophylaxis)" to "The primary endpoint, the ABR of all types of bleeding episodes, will be calculated for each subject and described for each regimen (on-demand and prophylaxis)."
Purpose for Change: To align with analysis criteria

23. Section 9 Research Methods
Description of Change: In "Data Analysis", in the "Primary Endpoint", description of statistical analysis was cancelled
Purpose for Change: To align with analysis criteria

24. Section 9 Research Methods
Description of Change: In "Data Analysis", in the "Primary Endpoint", the sentence "In addition, a separate descriptive efficacy analyses of ABR will be provided for each of the following independent treatment regimens, assuming minimum observed period is satisfied (≥90 days)" was changed to "Separate descriptive efficacy analyses of ABR will be provided for each of the following treatment regimens, assuming minimum observed period is satisfied (≥90 days)"
Purpose for Change: To align with analysis criteria

25. Section 9 Research Methods
Description of Change: In "Data Analysis", in the "Methods of Analysis for Other Primary Efficacy Criteria", the first paragraph has been simplified
Purpose for Change: To align with analysis criteria

26. Section 9 Research Methods
Description of Change: In "Data Analysis", in the "Methods of Analysis for Other Primary Efficacy Criteria", the sentence (title) "For treatment of bleeding episodes" was added; the word "independent" was removed from the following sentence; in the tables, the second and the third statistics analyses were changed from "Sum" to "Median(Q1,Q3); the sentence (title) "Assessment of efficacy" was removed; the sentence (title) "For prevention of bleeding episodes" was added; the following sentence was changed from" Corresponding to subjects given prophylaxis infusions (FEIBA NF) in this study, the following parameters and statistics will be computed by treatment regimen (prophylaxis, on-demand)" to "Corresponding to subjects given prophylaxis infusions or on-demand regimen (FEIBA NF) in this study, the following parameters and statistics will be computed by treatment regimen (prophylaxis, on-demand)"; the sentence "Efficacy will be assessed by a "excellent-to-poor" 4-point Likert scale by the subjects or care-giver at the end of each prophylaxis period (possibly rated within 24 hours from the end of the prophylactic treatment) or on an annual basis depending on which occurs first" was added.
Purpose for Changes: To make it consistent with analysis criteria

27. Section 9 Research Methods
Description of Change: In "Secondary Endpoints", the methods of analysis were changed as follows: the sentence "Linear interpolation (for any time interval) and line extrapolation (for up to 0.5 years) will be used to derive an estimate of the score at these timepoints" was removed from the first four bullet points
Purpose for Change: To align assessment with evaluation criteria

28. Section 9 Research Methods
Description of Change: In "Planned Interim Analysis of the Study" the description of the interim analysis was changed from "The first study interim analysis is planned after all subjects are enrolled and have completed 1 year of observation. A second study interim analysis is planned after all patients are enrolled and with whom have completed two years of observation. Regular safety updates and study progress reports are to be scheduled" to "The first study interim analysis is planned after all subjects are enrolled. All the following 3 interim study analyses will be available in May on annual basis in the period 2019-2021 Regular safety updates and study progress reports are to be scheduled"
Purpose for Change: To reflect updated estimation of Interim Study Reports

29. Sections 9.1.2.2, 9.3.2.1, 9.3.2.3, 9.7.3.5 and throughout the document
Description of Change: Removed text regarding additional local scoring instrument results being collected
Purpose for Change: To be aligned with CRF

30. Section 9.1.2.3, 9.3.3, 9.7.3.6
Description of Change: Removed number of ER visits
Purpose for Change: To be aligned with CRF

31. Section 11 Management and reporting of adverse events/adverse reactions
Description of Change: in "Serious Adverse Events", a new sub-bullet point was added: "Thrombotic microangiopathy".
Purpose for Change: As per PRAC recommendations and few Regulatory Agencies request

32. Section 11 Management and reporting of adverse events/adverse reactions
Description of Change: in "Untoward Medical Occurrences Not Considered Adverse Events", a new bullet point was added: "Elective surgeries: Elective and planned surgeries, when these surgeries relate to a preexisting disease (see also Section 11.2.6) that has not worsened during study participation, will not be considered as (S)AEs"
Purpose for Change: To clarify reporting rule for Elective surgeries

14.4.2 Protocol Amendment 1 (Version 25 Mar 2015) Changes

In this section, changes from the previous version of the Protocol, dated 2013 SEP 30, are described and their rationale is given.

Throughout the document

Description of Change: Change of sponsor name/entity.

Purpose for Change: Administrative.

INVESTIGATOR ACKNOWLEDGEMENT

FEIBA NF - FACTOR VIII INHIBITOR BY-PASSING ACTIVITY NANOFILTERED

FEIBA NF GLOBAL OUTCOME STUDY

(FEIBA-GO)

PROTOCOL IDENTIFIER: 091301

AMENDMENT 2: 2017 DEC 19

Replaces: Amendment 1 : 2015 MAR 25

ALL VERSIONS:

Amendment 2: 2017 DEC 19
Amendment 1: 2015 MAR 25
ORIGINAL: 2013 SEP 30

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing ethics committee(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Non-interventional Trial Agreement, good pharmacovigilance practices, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator