An 18-month low-interventional prospective, multicentre study to assess joint outcomes in patients with haemophilia A or B on prophylaxis with efmoroctocog alfa or eftrenonacog alfa

Protocol Version 1.0

Sponsor: Swedish Orphan Biovitrum AB, SE-112 76 Stockholm, Sweden

PROTOCOL CLARIFICATION MEMORANDUM #1

06 December 2022

Summary of Revision and Rationale:

The purpose of this protocol clarification memorandum is to clarify the EU trial number:

- Trial number 2022-003568-26 currently recorded on Protocol is the EudraCT number, mistakenly requested.
- The study will be submitted in accordance with Clinical Trials Regulation EU 536/2014 and recorded in the CTIS portal, therefore an EU trial number is needed.
- EU trial number is **2022-502921-16-00** and shall be used on all clinical trial documents where such number is required.

Implementation:

This modification will be implemented immediately.

The modification included in this Clarification Memorandum will be incorporated into the next full protocol amendment.

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PPD
Signing Reason: I approve this document
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An 18-month low-interventional prospective, multicentre study to assess joint outcomes in patients with haemophilia A or B on prophylaxis with efmoroctocog alfa or eftrenonacog alfa

JOIN-us

Protocol Version 1.0

EU trial number: 2022-003568-26

Type of Study: Therapeutic Use

Sponsor: Swedish Orphan Biovitrum AB, SE-112 76 Stockholm, Sweden

Sponsor's Medical Director	Principal Coordinating Investigator
PPD	PPD
DocuSigned by: PPD Signing Reason: I approve this document Signing Time: November 18, 2022 | 18:41:18 CET 0C77692135094D36930464498D92C3C7	DocuSigned by: November 19, 2022 | 09:24:30 CET PPD Motivo de la firma: Apruebo este documento Hora de firma: November 19, 2022 | 09:24:26 CET E060EA81E31A42E8A0A813E281635C7D
Signature Date	Signature Date

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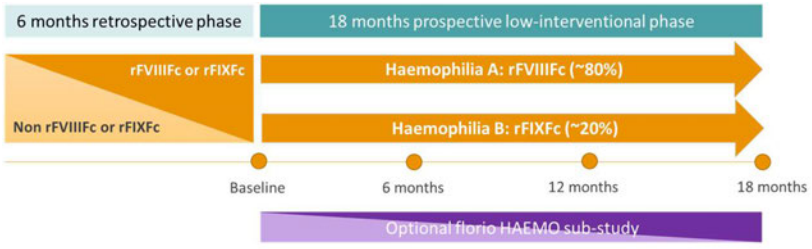
1 Synopsis

STUDY IDENTIFIERS	
Title of study:	An 18-month low-interventional prospective, multicentre study to assess joint outcomes in patients with haemophilia A or B on prophylaxis with efmoroctocog alfa or eftrenonacog alfa
Clinical study number:	Sobi.HAEM89-007
Type of study:	Therapeutic use
STUDY OBJECTIVES	
Primary objective:	To evaluate the overall joint status as detected by ultrasound (US) in haemophilia A and B patients treated with efmoroctocog alfa (rFVIIIFc) or eftrenonacog alfa (rFIXFc) prophylaxis over the 18-month study period.
Secondary objectives:	• To evaluate the joint status as detected by US in the Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) specific items of hypertrophic synovium, cartilage and bone damage in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period • To evaluate the clinical joint status as detected by Hemophilia Joint Health Score (HJHS) in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period • To evaluate the presence, resolution, recurrence and new development of target joints in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over 18 months • To describe the bleeding episodes in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period • To evaluate the quality of life in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period
Exploratory objectives – florio® HAEMO sub-study:	• Impact of florio HAEMO on patients' sense of protection and their physical activity level in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis • Explore adherence to prescribed treatment regimen in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis • Explore relationship between estimated FVIII and FIX levels and physical activity in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis • Explore timing of bleeding episodes in relation to estimated FVIII and FIX levels and physical activity in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis • Explore the use of florio HAEMO to characterise pain and well-being in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis
STUDY ENDPOINTS	
Primary endpoint:	• Change from baseline in total HEAD-US score up to month 18 (end of study - EOS).

Secondary endpoints:	• Change from baseline in HEAD-US score for hypertrophic synovium at 6, 12 and 18 months • Change from baseline in HEAD-US score for cartilage at 6, 12 and 18 months • Change from baseline in HEAD-US score for bone at 6, 12 and 18 months • Change from baseline in total HJHS at month 18 (EOS) • Number and location of target joints at baseline, 6, 12 and 18 months • Total Annualized bleeding rate (ABR), joint ABR, target joint ABR, traumatic/spontaneous ABR • Patient-Reported Outcomes Measurement Information System (PROMIS) physical function/activity scores at baseline and 18 months • PROMIS pain intensity and interference scores at baseline and 18 months • IPAQ-SF scores at baseline and 18 months
Exploratory endpoints – florio HAEMO sub-study:	• Results from questionnaire on impact of florio HAEMO tools on patients' sense of protection and their physical activity level • florio HAEMO captured treatment adherence scores • florio HAEMO captured estimated FVIII and FIX levels • florio HAEMO captured physical activity type, duration and intensity • florio HAEMO captured bleed data (timing, location, cause, treated/untreated) • florio HAEMO captured FVIII/FIX administration data (time, dose) • florio HAEMO captured pain data (time, location, cause, intensity) • florio HAEMO captured well-being data
STUDY DESIGN AND METHODS	
Study design:	This is a prospective, low-interventional, single-arm, multicentre study to describe the joint health over an 18-month period of prophylactic treatment with rFVIIIFc or rFIXFc in patients with haemophilia A or haemophilia B in a real-world setting. Approximately 250 patients will be enrolled in the study. Around 80% of the patients are expected to have haemophila A and around 20% haemophila B. Retrospective data from patient medical records will be collected for at least 6 months before enrolment in the study. From enrolment and throughout the study, patients will perform on-site study visits at 6-month intervals. Each patient is expected to actively participate in the study for 18 months (from baseline to EOS visit). Joint health will be assessed with HEAD-US and HJHS scoring. Quality of life and physical activity will be assessed with Patient-reported outcomes (PROs). Patients will be on prophylactic treatment with rFVIIIFc or rFIXFc according to usual clinical practice and the dosing guide in the respective Summary of Product Characteristics (SmPC). Choice of treatment will not be dictated by the study protocol. 

Number of patients planned:	Approximately 250. Around 80% of the patients are expected to have Haemophila A and around 20% Haemophila B.
Diagnosis and main criteria for inclusion:	A patient must fulfill the following criteria in order to be included in the study: 1. Age ≥ 6 years 2. Diagnosis of haemophilia A or B 3. Having at least 6 months documented pre-study treatment data regarding treatment prescriptions and bleeding episodes prior to the baseline visit 4. Previous treatment for haemophilia A or B with any marketed recombinant and/or plasma-derived FVIII or FIX concentrate for at least 6 months 5. Start of prophylactic treatment with rFVIIIFc or rFIXFc prior to study enrolment or latest at the baseline visit, in accordance with local regulations 6. Signed and dated informed consent provided by the patient, or the patient's legally authorized representative for patients under the legal age. Assent should be obtained from paediatric patients in accordance with local regulations **florio HAEMO sub-study** To be eligible for the florio HAEMO sub-study a patient should have used florio HAEMO (a CE marked medical device used in routine clinical practice) for at least 3 months and must agree to have data collected from the florio HAEMO app by providing a separate informed consent or assent.
Assessments:	• At each visit HEAD-US assessments will be performed. Information on pain, anti-inflammatory and anti-depressant medications will be recorded • At enrolment/baseline and EOS, PROs will be completed • At enrolment/baseline and EOS, HJHS will be assessed • For patients participating in the florio HAEMO sub-study a questionnaire on the impact of florio HAEMO on patients' sense of protection and their physical activity level will be administered when they enter the sub-study. Data from the florio HAEMO app will be collected **Safety Assessments:** The following safety events should be collected: • Serious Adverse Events (SAEs) • Non-serious Adverse Events (AEs) assessed as causally related to treatment with rFVIIIFc or rFIXFc and considered unexpected • AEs of special interest: inhibitor development, thrombotic events and serious hypersensitivity reaction including anaphylactic reactions • AEs leading to premature discontinuation of rFVIIIFc or rFIXFc • Exposure during pregnancy, medication errors, misuse or abuse in relation to rFVIIIFc or rFIXFc Any AE suspected to be causally related to a medicinal product other than the studied Sobi product, and which does not result from a possible interaction with it, should be reported by the Investigator to the concerned authority via the national reporting system, or to the Marketing Authorization Holder of the suspected medicinal product.

<table>
<tr><td>Test product; dose and mode of administration:</td><td>N/A</td></tr>
<tr><td>Reference product; dose and mode of administration:</td><td>N/A</td></tr>
<tr><td>Auxiliary medicinal products:</td><td>N/A</td></tr>
<tr><td>Duration of treatment(s):</td><td>According to routine clinical practice</td></tr>
<tr><td>Determination of sample size:</td><td>With a sample size of 250 patients (200 with Haemophilia A and 50 with Haemophilia B) assuming a standard deviation of 13, the mean change from baseline in Total HEAD-US score will be estimated with a level of accuracy that is lower than a clinically meaningful worsening of 2, e.g. a half width of 1.61.
<table>
<tr><th>Confidence level</th><th>Standard deviation</th><th>n</th><th>Half width</th></tr>
<tr><td>95%</td><td>7</td><td>250</td><td>0.87</td></tr>
<tr><td>95%</td><td>10</td><td>250</td><td>1.25</td></tr>
<tr><td>95%</td><td>13</td><td>250</td><td>1.61</td></tr>
<tr><td>95%</td><td>13</td><td>200</td><td>1.80</td></tr>
</table></td></tr>
<tr><td>Statistical methods:</td><td>No formal hypothesis testing will be performed. Mean change from baseline will be estimated using a generalized linear mixed model with repeated measures, adjusted for clinically important covariates.
All continuous variables will be summarized with descriptive statistics including number of observations, mean, standard deviation, median, quartiles, minimum and maximum values. Categorical variables will be summarized in frequency tables including number of observed responses in each category as well as percentages. Number of missing observations will also be displayed. No formal statistical hypothesis testing is planned.
Subgroups will be created to further explore the endpoints e.g. for age, severity of haemophilia, type of haemophilia, presence of joint disease at inclusion, and intensity of treatment.</td></tr>
</table>

2 Abbreviations and definition of terms

2.1 List of Abbreviations and definitions

Term	Definition
ABR	Annualized bleeding rate
AE	Adverse event
Bleeding episode	A bleeding episode starts from the first sign/symptom of bleeding as reported by the patient and ends no more than 72 hours after the last injection to treat the bleeding episode (1). Any subsequent bleeding at the same location and injections administered ≤72 hours from the previous injection will be considered as the same bleeding episode. Multiple bleeding locations treated with a single injection will also be considered a single bleeding episode. Any injection to treat the bleeding episode that is administered >72 hours after the preceding one will be considered the first injection to treat a new bleeding episode in the same location. Any injection used to treat subsequent bleeding at a different location will be considered a separate bleeding episode, regardless of the time from the last injection to treat a bleeding episode.
BU	Bethesda unit
CDISC	Clinical data interchange standards consortium
CRO	Contract research organization
(e)CRF	(electronic) Case report form
EOS	End of study
EDC	Electronic data capture
EU	European Union
FAS	Full analysis set
FIX	Factor IX
FVIII	Factor VIII
GCP	Good clinical practice
GPV	Global pharmacovigilance & patient safety
Haemophilia severity	Mild haemophilia: >5 IU/dL to <40 IU/dL endogenous factor VIII/IX

Term	Definition
	Moderate haemophilia: 1 to 5 IU/dL endogenous factor VIII/IX Severe haemophilia: <1 IU/dL endogenous factor VIII/IX
HEAD-US	Haemophilia Early Arthropathy Detection with Ultrasound
HRQoL	Health-related quality of life
HJHS	Hemophilia Joint Health Score
ICH	International council for harmonisation
IEC	Independent ethics committee
IPAQ-SF	International Physical Activity Questionnaire - Short Form
Impaired joint	Any joint that has persistent functional or structural abnormalities, considered clinically relevant by the Investigator, with or without bleeding episodes.
Index joint	Ankle, knee, elbow (left and right)
Major surgery	Any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, operation in joint, or dental extraction of any molar teeth or ≥3 nonmolar teeth).
Minor surgery	Any surgery that do not fall under the definition of Major surgery
MRI	Magnetic resonance imaging
NIH	National Institute of Health
PP	Per Protocol
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System (PROMIS®)
rFVIIIFc	Efmoroctocog alfa (a recombinant FVIII Fc fusion protein, Elocta®)
rFIXFc	Eftrenonacog alfa (a recombinant FIX Fc fusion protein, Alprolix®)
ROM	Range of motion

Term	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
Sobi	Swedish Orphan Biovitrum AB (publ)
SUSAR	Suspected unexpected serious adverse reaction
Target joint	Three or more spontaneous bleeds into a single joint within a consecutive 6-month period. Where there have been ≤2 bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint (1) Recurrence is defined as ≥3 spontaneous bleeds in a single joint within any consecutive 6-month period after target joint resolution.
US	Ultrasound

3 Ethics

3.1 Independent ethics committee

It is the responsibility of the investigator to ensure approval of the study protocol, possible amendments and the written patient information and informed consent form from the Independent ethics committee (IEC) before commencing the study. The investigator should file all correspondence with the IEC as applicable. Copies of IEC correspondence and approvals should be forwarded to the Contract research organization (CRO).

3.2 Ethical consideration of the study

This study will be conducted in compliance with this protocol, the International council for harmonisation Good clinical practice (ICH GCP) (2), European regulation 536/2014 (3) for clinical studies, other applicable regulatory requirements, and in accordance with the ethical principles that have their origin in the 2013 version of the Declaration of Helsinki) (4).

3.3 Patient information and consent

It is the responsibility of the investigator or designee to give each patient (or the patient's acceptable representative) prior to any study-related activities, full and adequate verbal and

written information regarding the objective and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time.

The written patient information and/or informed consent/assent form must not be changed without prior discussion with Swedish Orphan Biovitrum AB (publ) (Sobi). Before any revisions are implemented, the revised written patient information and/or informed consent form must be approved by the IEC.

It is the responsibility of the investigator or designee to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all patients prior to any study-related activities. The patients should receive a copy of the written information, the signed informed consent form and assent form for patients not being able to provide full consent (i.e. minors). Patients who become adults during the study duration will be re-consented as applicable in accordance with local regulations.

For patients willing to participate in the florio® HAEMO sub-study (see section 6.5.11), a separate consent will be obtained.

4 Introduction

4.1 Background

Haemophilia is a rare genetic disorder characterized by a deficiency in coagulation factor VIII (FVIII; haemophilia A) or factor IX (FIX; haemophilia B) causing impaired haemostasis and prolonged bleeding episodes. Severe haemophilia, defined as <1% of normal Factor VIII/FIX activity in haemophilia A and haemophilia B respectively, occurs in approximately 45% of haemophilia A and approximately 35% of haemophilia B patients, and results in frequent and spontaneous bleeds into muscles and joints, commonly the elbows, knees, and ankles (5, 6, 7). Bleeding into joints can cause acute pain and swelling and can result in reduced joint range of motion (ROM), long-term cartilage damage and haemophilic arthropathy (5). As a result of bleeding episodes and resulting progressive joint damage, haemophilia patients experience decreased physical functioning, pain, and poor health-related quality of life (HRQoL) (8).

The cornerstone of haemophilia treatment in patients with haemophilia A and B is FVIII or FIX prophylaxis, respectively, to prevent and control bleeding episodes and, consequently, prevent or slow down the development of arthropathy. In fact, joint damage and progressive chronic arthropathy are the hallmarks of haemophilia because a single or few repeated joint bleeds can lead to structural joint damage due to synovial inflammation caused by haemosiderin deposition (9). Synovial iron deposition and inflammatory cell proliferation provokes degeneration of joint surfaces and eventually loss of normal joint function (9, 10) and may lead to disabling arthropathy. In addition to its efficacy for arthropathy prevention, FVIII or FIX prophylaxis has been associated with improvements in HRQoL and opportunities for a more physically active life (11, 12).

Extended half-life products used for replacement factor therapy have been developed utilizing Fc or albumin fusion technology, or pegylation, to prolong their half-life (13). Efmoroctocog alfa [a recombinant FVIII Fc fusion protein, Elocta®] (rFVIIIFc) and Eftrenonacog alfa [a recombinant FIX Fc fusion protein, Alprolix®] (rFIXFc) are recombinant coagulation factor concentrates with extended half-life. In contrast to standard half-life factor replacement products, the addition of the Fc region of human immunoglobulin G1 (IgG1) to the recombinant factor allows rFVIIIFc and rFIXFc to bypass lysosomal degradation and remain circulating in the bloodstream longer than standard half-life factor replacement products, thus prolonging the plasma terminal half-life. rFVIIIFc first received market authorization in June 2014 in the US, for the treatment of haemophilia A. Thereafter, in November 2015, it received market authorization in the European Union (EU) under the tradename Elocta®. rFIXFc first received market authorization in the US March 2014 and then in Europe in May 2016 for the treatment of haemophilia B under the tradename Alprolix®.

Despite the use of prophylaxis many patients still experience joint bleeds which may lead to joint deterioration over time (14, 15). Furthermore, not all bleeds may be clinically evident, as there are indications of subclinical bleeds in patients receiving treatment for their haemophilia (16). It is therefore important to gather additional information on the joint health of haemophilia patients using currently available examination methods.

Thorough examination of the joints and follow-up of patients is a crucial part of patient management and helps to identify when there is a need to adjust the treatment regimen. There are currently several examination methods to identify joint damage early on, including clinical joint examination and different imaging techniques. The functional Hemophilia Joint Health Score (HJHS) (17, 18, 19) for clinical joint assessment and more recently the Haemophilia Early Arthropathy Detection with UltraSound (HEAD-US) protocol for joint imaging are two established examinations.

The HEAD-US protocol has been developed for non-radiologists to assess synovial hypertrophy and cartilage defects using point-of-care ultrasound (US) examination, enabling direct assessment of joint health in conjunction with medical history and physical examination (20). The HEAD-US scoring method is based on an additive scale with assessment of ankles, knees and elbows. It includes indicators of disease activity (synovitis; hypertrophic synovium) and structural osteochondral damage (articular cartilage and subchondral bone).

Strengthening muscles can help improve joint health by reducing impacts on joints, and participation in sporting activities may help individuals compensate for motor skill deficits that arise because of complications of haemophilia, such as arthropathy (21). Among adults with haemophilia, regular physical activity helps prevent obesity and other chronic conditions; in children and adolescents with haemophilia, physical exercise supports joint, bone, and muscle health; weight control; and anxiety reduction (22).

However, patients may limit their physical activities due to fear of bleeding if they are unaware of their current FVIII or FIX level. Patient apps and wearables are now available which allow patients to view their estimated FVIII or FIX levels, and capture health-related data (such as bleeding episodes, pain, well-being, physical activity levels etc.).

These data can be shared with the treating physician supporting the planning to individualize the patient's factor treatment based on current lifestyle, health status and physical activity levels.

florio HAEMO, a CE marked medical device used as part of routine clinical practice, consists of the florio HAEMO app (for patients with haemophilia and/or their caregivers) and the florio HAEMO dashboard (for healthcare professionals).

Synovitis is currently considered a marker of haemophilia activity and can be unnoticed on physical examination, especially in patients on prophylaxis. Performing point-of-care US examination is considered as the most practical option for regular monitoring of joints to detect soft tissue and osteochondral changes, and physical examination provide complementary information on the joint disease.

Favourable joint outcomes are expected with modern haemophilia A and haemophilia B management. However, evaluation of long-term treatment outcomes is hampered by the delay between bleeding episodes during childhood and resulting joint outcomes in adulthood. Future research with combined US and/or Magnetic resonance imaging (MRI) is needed to better understand joint outcomes. Ultrasound paired with physical examination increases the sensitivity for detection of joint damage (23). Accordingly, the expected joint health outcomes, based on HEAD-US scoring, in patients receiving adequate prophylactic treatment is at least the maintenance of a stable joint status or the improvement in reversible lesions for the patients with already established joint damage.

4.2 Study rationale

The efficacy and safety of rFVIIIFc and rFIXFc have been established in clinical trials as required for regulatory approvals. In addition, several completed and ongoing non-interventional studies describe the effectiveness and usage of rFVIIIFc and rFIXFc in the real-world setting (24, 25). However, there are still limited real-world data on joint health outcomes, assessed with objective measures, in patients receiving rFVIIIFc or rFIXFc prophylaxis.

The main purpose of this study is to prospectively describe the joint health over an 18-month period of prophylactic treatment with rFVIIIFc or rFIXFc in patients with haemophilia A or haemophilia B in a real-world setting in Europe. This is a low-interventional, multicentre study using point-of-care US examination for regular monitoring of soft tissue and osteochondral changes in the joints, as well as physical examination as a complementary assessment of joint disease.

Data output from florio HAEMO, and patient feedback via a patient questionnaire on physical activity levels and sense of protection while using florio HAEMO, will be analyzed as exploratory objectives in a sub-study. This sub-study will explore possible correlations between the levels of physical activity, the estimated FVIII/FIX levels and bleeding occurrence.

4.3 Potential risks and benefits

This is a low-interventional study. While joint assessments with HEAD-US and HJHS may be part of the patient's usual routine clinical care, the study specific requirement to complete these assessments according to the study's schedule of events is considered a low intervention. The completion of Patient-reported outcomes (PROs) is also considered a low intervention. These interventions are not assessed to pose more than minimal risk to the patients.

rFVIIIFc and rFIXFc have marketing authorization and will be used per approved indication. They will be prescribed independently from the decision to enrol a patient in the study, and choice of treatment is hence not dictated by the study protocol.

Participation is not expected to have any particular benefit for the enrolled patients, other than a potentially more intensive follow-up by their physician. The results from the study may help in improving the knowledge of joint disease and US assessment in patients with haemophilia, and potentially in improving the management of haemophilic arthropathy in the future.

5 Study objectives and endpoints

5.1 Primary objective

To evaluate the overall joint status as detected by ultrasound in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period.

5.1.1 Primary endpoint

Change from baseline in total HEAD-US score up to month 18 (EOS).

5.2 Secondary objectives

- To evaluate the joint status as detected by ultrasound in the HEAD-US specific items of hypertrophic synovium, cartilage and bone damage in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period
- To evaluate the clinical joint status as detected by HJHS in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period
- To evaluate the presence, resolution, recurrence and new development of target joints in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over 18 months
- To describe the bleeding episodes in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period
- To evaluate the QoL in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period

5.2.1 Secondary endpoints supporting the secondary objective(s)

- Change from baseline in HEAD-US score for hypertrophic synovium at 6, 12 and 18 months
- Change from baseline in HEAD-US score for cartilage at 6, 12 and 18 months
- Change from baseline in HEAD-US score for bone at 6, 12 and 18 months
- Change from baseline in total HJHS at month 18 (EOS)
- Number and location of target joints at baseline, 6, 12 and 18 months
- Total Annualized bleeding rate (ABR), joint ABR, target joint ABR, traumatic/spontaneous ABR
- Patient-Reported Outcomes Measurement Information System (PROMIS) physical function/activity scores at baseline and 18 months
- PROMIS pain intensity and interference scores at baseline and 18 months
- International Physical Activity Questionnaire - Short Form (IPAQ-SF) scores at baseline and 18 months

5.3 Exploratory objectives – florio HAEMO sub-study

- Impact of florio HAEMO on patients' sense of protection and their physical activity level in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis
- Explore adherence to prescribed treatment regimen in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis
- Explore relationship between estimated FVIII and FIX levels and physical activity in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis
- Explore timing of bleeding episodes in relation to estimated FVIII and FIX levels and physical activity in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis
- Explore the use of florio HAEMO to characterise pain and well-being in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis

5.3.1 Exploratory endpoints

- Results from questionnaire on impact of florio HAEMO tools on patients' sense of protection and their physical activity level
- florio HAEMO captured treatment adherence scores
- florio HAEMO captured estimated FVIII and FIX levels
- florio HAEMO captured physical activity type, duration and intensity
- florio HAEMO captured bleed data (timing, location, cause, treated/untreated)
- florio HAEMO captured FVIII/FIX administration data (time, dose)
- florio HAEMO captured pain data (time, location, cause, intensity)
- florio HAEMO captured well-being data

6 Investigational plan

6.1 Overall study design and plan

This is a prospective, low-interventional, single-arm, multicentre study to describe the joint health over an 18-month period of prophylactic treatment with rFVIIIFc or rFIXFc in patients with haemophilia A or haemophilia B in a real-world setting. Approximately 250 patients will be enrolled in the study. Around 80% of the patients are expected to have haemophila A and around 20% haemophila B.

Retrospective data from patient medical records will be collected for at least 6 months before enrolment in the study. From enrolment and throughout the study, patients will perform on-site study visits at 6-month intervals. Each patient is expected to actively participate in the study for 18 months (from baseline to end of study [EOS] visit).

Joint health will be assessed with HEAD-US and HJHS scoring. Quality of life and physical activity will be assessed with PROs. Patients will be on prophylactic treatment with rFVIIIFc or rFIXFc according to usual clinical practice and the dosing guide in the respective Summary of Product Characteristics (SmPC). Choice of treatment will not be dictated by the study protocol.

The recruitment period is planned to be approximately 12 months from the timepoint when the first patient is enrolled in the study. Around 60 sites in approximately 11 European countries are expected to participate in the study.

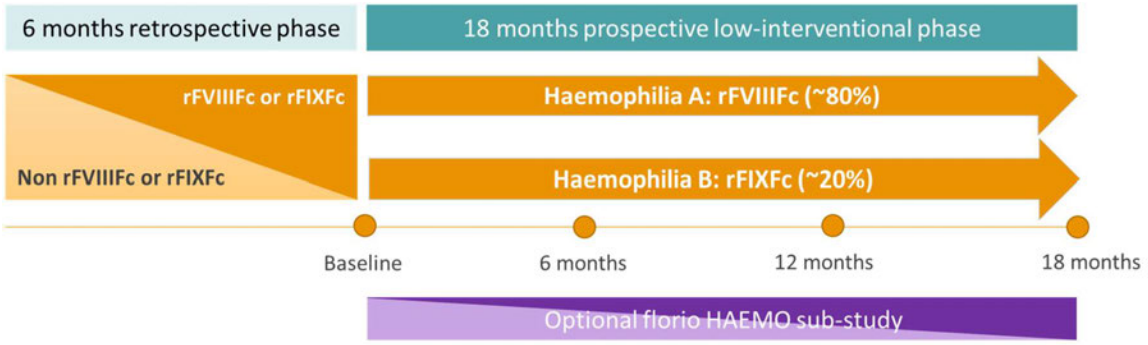
No specific evaluation committees will be utilized for this study, since it is a low-interventional study having no interventions posing more than minimal risk to the patients.

Interim analyses are planned to be performed during the study. The first interim analysis is to be performed once recruitment is completed. The purpose of the first interim analysis is to assess the baseline variability of HEAD-US score results and to share baseline characteristics with the haemophilia community. The second interim analysis is planned to be performed once at least 50% of the patients have completed their 12-month visit and will evaluate the joint health status at that time.

In an optional, exploratory sub-study, data will be collected via the florio HAEMO app. All exploratory endpoints and objectives in the study are related to the exploratory sub-study.

The overall study design is described in Figure 1.

Figure 1 Study Design



6.2 Discussion of study design, including the choice of control groups

This prospective, low-interventional, multicentre study is being conducted to describe the joint health over an 18-month period in patients on prophylactic treatment with rFVIIIFc or rFIXFc with haemophilia A or haemophilia B in a real-world setting. The 18-month follow-up period is considered to be long enough to see changes and/or show medium/long-term stabilization of joint status. Patients treated on demand are not included in the study, as this would lead to a too high variability in the patient population.

Joint outcomes will be described over time and reported in a quantitative/objective manner with HEAD-US and HJHS scores. These assessments are not always fully incorporated in routine clinical practice and are therefore intended to be investigated in the low-interventional setting of this study. Both examinations have been chosen due to their complimentary features – HJHS is a clinical assessment focused on functionality and HEAD-US is a more sensitiveUS assessment with the ability to detect structural joint damage and synovitis earlier on in the joint deterioration.

This study will not have a control group. The reason for this is that it is not considered needed to be able to evaluate the primary objective of the study.

Patients excluded from participation in this study (section 6.3.2) will have been assessed as not being suitable for the study.

6.2.1 Patient input into design

Representatives from patient organizations in six countries – Czech Republic, France, Germany, Italy, Spain and Sweden, joined Patient Council meetings and provided input on the study design which included objectives and endpoints, PRO scales, visit schedule and study assessments. Their feedback resulted in the decision on the PROs to be used in the study and their format, and also influenced the decision on study duration. The group appreciated a study with focus on both joint health and pain.

6.3 Selection of study population

Children from the age of six are allowed to be enrolled in the study. To enrol children in this type of study is considered justified since the study is not posing more than minimal risk to the participating patients and signs of joint damage due to haemophilia are known to develop from an early age. It is judged that children from the age of six are able to comply with study procedures without any major impact on their daily life.

Prospective approval of a protocol deviation to recruitment and enrolment criteria, also known as protocol waiver or exemption, is not permitted.

6.3.1 Inclusion criteria

A patient must fulfill the following criteria in order to be included in the study:

1. Age ≥ 6 years
2. Diagnosis of haemophilia A or B
3. Having at least 6 months documented pre-study treatment data regarding treatment prescriptions and bleeding episodes prior to the baseline visit
4. Previous treatment for haemophilia A or B with any marketed recombinant and/or plasma-derived FVIII or FIX concentrate for at least 6 months
5. Start of prophylactic treatment with rFVIIIFc or rFIXFc prior to study enrolment or latest at the baseline visit, in accordance with local regulations
6. Signed and dated informed consent provided by the patient, or the patient's legally authorized representative for patients under the legal age. Assent should be obtained from paediatric patients in accordance with local regulations

6.3.1.1 florio HAEMO sub-study

To be eligible for the florio HAEMO sub-study a patient should have used florio HAEMO (a CE marked medical device used in routine clinical practice) for at least 3 months and must agree to have data collected from the florio HAEMO app by providing a separate informed consent or assent.

6.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Any medical condition which in the opinion of the investigator makes the patient unsuitable for inclusion
2. Prophylactic treatment with non-factor therapy during the 6 months prior to enrolment
3. Presence of factor VIII or FIX inhibitory antibodies (inhibitors) (≥0.60 Bethesda Units [BU]/mL) at the latest available inhibitor test
4. Enrolment in a concurrent clinical interventional study, or intake of an Investigational medicinal product, within 3 months prior to inclusion in this study

5. Foreseeable inability to cooperate with given instructions or study procedures

6.3.3 Withdrawal of patients from study

6.3.3.1 Withdrawal from study

Whenever possible and irrespective of the reason for withdrawal, the patient should be examined as soon as possible. All relevant assessments should be completed, preferably according to the schedule of events (see section 6.5.1.1). The Case report form (CRF) should be completed as far as possible. Date and reason for the study withdrawal should be clearly described in the CRF.

A patient should be withdrawn from the study for any one of the following reasons:

- The patient develops factor VIII or FIX inhibitory antibodies (inhibitor titre ≥0.60 BU/mL)
- The patient or his legally authorized representative(s) withdraws consent
- The patient enrols into an interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered
- The patient enrols into a low-interventional clinical study where the assessments performed are of such nature that the patient cannot be considered treated per usual routine practice
- The patient discontinues prophylactic treatment with rFVIIIFc or rFIXFc
- The patient is no longer willing to undergo the mandatory US examination

If any Adverse Event (AE) is associated with the withdrawal this should be recorded in the CRF.

If the patient withdraws consent for disclosure of future information (data, samples), the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Patients will not be withdrawn if they miss a study visit.

If a patient withdraws from the study and more than 3 months since the last study visit have passed, all assessments should be performed to the extent possible. If a patient withdraws from the study less than 3 months since the last visit, PRO collection and HJHS assessment should be performed to the extent possible.

6.3.4 Replacement of withdrawn patients

Withdrawn patients will not be replaced.

6.4 Study treatment(s) and concomitant therapy

Study treatments/interventions are all pre-specified interventions (e.g., clinical assessments and behavioral) intended to be administered to the study participants during the study conduct.

Both rFVIIIFc and rFIXFc will be used as per clinical routine for each patient and their use will not be dictated by the protocol.

6.4.1 Prior and concomitant therapy

Therapies considered necessary for the patient's welfare may be given at the discretion of the investigator. Pain, anti-inflammatory and anti-depressant therapies used in the month preceding baseline/every follow-up visit must be recorded in the CRF. No medicinal product under investigation may be used in this study.

6.4.2 Treatment compliance

Treatment compliance, as assessed by the investigator, will be recorded in the CRF.

6.5 Effectiveness and safety assessments

6.5.1 Study schedule

6.5.1.1 Schedule of events

Tests and Assessments	Enrolment Visit (Visit 0)[1]	Baseline Visit (Visit 1)[1]	Follow-up Visits		
			Month 6 (Visit 2) *(± 28 days)*	Month 12 (Visit 3) *(± 28 days)*	Month 18, End of Study (Visit 4) *(- 28 days and + 56 days)*
Informed Consent and Assent	X	X			
Review of eligibility criteria	X	X			
Sex	X	X			
Age	X	X			
Height	X	X	X[2]	X[2]	X[2]
Weight	X	X	X	X	X
Haemophilia history	X	X			
Medical and surgical history	X	X			
Information on surgery, including joint surgery, and interventions	X	X	X	X	X

Tests and Assessments	Enrolment Visit (Visit 0)[1]	Baseline Visit (Visit 1)[1]	Follow-up Visits		
			Month 6 (Visit 2) *(± 28 days)*	Month 12 (Visit 3) *(± 28 days)*	Month 18, End of Study (Visit 4) *(- 28 days and + 56 days)*
Pain, anti-inflammatory and anti-depressant therapies used in the month preceding baseline/ at every follow-up visit	X	X	X	X	X
Bleeding information[3]	X[4]	X[4]	X	X	X
Prescribed rFVIIIFc or rFIXFc dose and injection frequency	X[4]	X[4]	X	X	X
Reason for change of haemophilia treatment *(if applicable)*	X	X	X	X	X
Factor rFVIIIFc or rFIXFc plasma activity levels, if available	X[4]	X[4]			X
Ultrasound (HEAD-US) score	X	X	X	X	X
Hemophilia Joint Health Score (HJHS)	X	X			X
Target joints presence and location	X	X			
Impaired joints presence and location	X	X			
PROs	X	X			X

Tests and Assessments	Enrolment Visit (Visit 0)[1]	Baseline Visit (Visit 1)[1]	Follow-up Visits		
			Month 6 (Visit 2) *(± 28 days)*	Month 12 (Visit 3) *(± 28 days)*	Month 18, End of Study (Visit 4) *(- 28 days and + 56 days)*
Physician judgement of patient's treatment adherence to rFVIIIFc or rFIXFc	X[4]	X[4]	X	X	X
Data from florio HAEMO *(estimated FVIII and FIX levels, physical activity levels, duration and type, bleeding episodes, pain, well-being, rFVIIIFc/rFIXFc dosing and adherence)*[5]	X	X	X	X	X
Questionnaire on impact of florio HAEMO on patients' sense of protection and their activity level	X[6]	X[6]			
Safety assessments[7]		X	X	X	X
SAEs[8]	X	X	X	X	X

Abbreviations: HEAD-US: haemophilia early arthopathy detection with ultrasound; HJHS: hemophilia joint health score; PRO: patient-reported outcome; SAE: serious adverse event

1. The enrolment and baseline visit may be performed either on the same day or divided over more than one day. Assessments should only occur once, i.e. no repeat measurements are needed for an assessment performed at enrolment. A time window of +28 days from the enrolment visit is allowed, if it is not possible to perform all assessments at the same time.
2. For patients younger than 18 years of age, height is recorded at all routine clinical visits. For adult patients, height is only recorded at the enrolment visit.
3. With the following captured for each bleeding episode, if available: bleeding episode circumstance (e.g. spontaneous, traumatic, surgery), bleeding location (e.g. muscle, elbow, knee, ankle, other), date of bleeding, number of injections to treat the bleeding episode, and dose (IU) used to treat the bleeding episode.
4. Including the 6-month period prior to enrolment
5. For patients who have used florio HAEMO for at least 3 months and consented to the use of data from florio HAEMO. Data will be retrospectively collected from the 6-month period prior to enrolment in the sub-study/main study, and until end of study.

6. Patients participating in the florio HAEMO sub-study will be asked to complete a questionnaire once. It can occur at baseline or any time during the main study, if they enrol in the sub-study after the baseline visit.
7. Refer to section “safety assessments” for the safety events to be captured.
8. All SAEs (including medically important AEs) from the Enrolment visit to the patient’s last study visit.

6.5.1.2 Visit 0/1 – Enrolment/Baseline

In this study, assessments related to enrolment and baseline may be performed either on the same day or divided over more than one day, depending on the availability of the patient and the site personnel. A time window of +28 days from the enrolment visit is allowed, if it is not possible to perform all assessments at the same time. No assessments may be performed prior to obtaining signed informed consent. The date when the HEAD-US assessment is performed will be considered as the baseline visit date and will be used to calculate the timepoints for the follow-up visits.

At the enrolment visit and prior to any study-related activities the patient/the patient's legally authorized representative have to sign and date the informed consent form.

The inclusion and exclusion criteria will be reviewed and recorded (see sections 6.3.1 and 6.3.2).

Data will be collected in accordance with the schedule of events (see section 6.5.1.1).

6.5.1.3 Visit 2 – Month 6

Data will be collected in accordance with the schedule of events (see section 6.5.1.1).

All study assessments should be performed within a ±28 days time window.

6.5.1.4 Visit 3 – Month 12

Data will be collected in accordance with the schedule of events (see section 6.5.1.1).

All study assessments should be performed within a ±28 days time window.

6.5.1.5 Visit 4 – Month 18/End of study

Data will be collected in accordance with the schedule of events (see section 6.5.1.1).

All study assessments should be performed within a -28 and +56 days time window. The date of the last assessment should be considered as the EOS date.

If a patient prematurely withdraws from the study and more than 3 months since the last study visit have passed, all assessments should be performed to the extent possible. If a patient withdraws from the study less than 3 months since the last visit, PRO collection and HJHS assessment should be performed to the extent possible.

6.5.2 Demography

Demographics includes age at screening (year of birth), sex, weight and height. The body weight recordings will be repeated at each visit. Height will be measured at the baseline visit for all patients, thereafter only for patients <18 years old. Body mass index will be calculated based on the weight and height measurements.

6.5.3 Haemophilia history

Haemophilia history will be collected at the baseline/enrolment visit including the following:

- severity of disease
- type of haemophilia
- age at diagnosis
- inhibitor history
- type of prophylactic treatment (primary, secondary or tertiary prophylaxis)
- age at prophylaxis initiation
- haemophilia prescription information (product, regimen, and dosing) from the 6 months period prior to enrolment
- haemophilia prescription information (product, regimen, and dosing) at time of enrolment
- previous non-factor therapy (product, start and stop date)
- bleeding episodes (location, spontaneous/traumatic) from the 6 months prior to enrolment
- date of first injection with rFVIIIFc or rFIXFc

6.5.4 Medical and surgical history

Significant medical and surgical history during at least the previous 6 months before enrolment will be collected.

Medical history includes any significant medical condition, including the following:

- history of allergy/anaphylactic shock
- HIV
- hepatitis B and C infection status
- clinically significant liver, renal, cardiovascular diseases
- clinical depression
- non-haemophilic acute or chronic medical conditions causing mobility/joint problems
- other coagulation disorder(s) in addition to haemophilia A or B

For surgical history, orthopaedic or musculoskeletal surgical or other interventions are of special interest. Information on date and type of intervention will be collected; for surgical interventions also classification in major/minor.

Data on surgical and other interventions related to joints will be collected for all joints and for anytime in the past.

6.5.5 Surgical and other interventions

Information on joint related surgeries and other interventions (including, but not limited to orthopaedic interventions, synoviorthesis (radio- and chemical)) will be collected. Moreover, any additional joint assessments including MRI, X-ray, and ROM will be documented. Information

on non-joint related surgeries, including tooth extractions, (type, date, classification (major/minor), related bleeding episodes) will be separately collected.

6.5.6 Target and impaired joints

At baseline, information on target joints (presence and location) will be recorded as per the assessment of the investigator. For the follow-up visits, resolution/reccurence/development of target joints will be calculated based on the investigator reported bleeds, as per the target joint definitions for resolution, recurrence and development (1).

Information on the presence, location and related assessments of impaired joints will be recorded as per the assessment of the investigator. A joint can simultaneously be a target joint and an impaired joint. The status of an impaired joint will be assessed at the baseline visit, and details on clinical/functional investigations performed as well as any changes in e.g. pain will be collected.

6.5.7 Concomitant therapy

Pain, anti-inflammatory and anti-depressant therapies used in the month preceeding baseline/ every follow-up visit will be collected.

6.5.8 Bleeding episodes

For any bleeding episode, the following will be collected:

- bleeding episode circumstance (e.g. spontaneous, traumatic)
- bleeding episode location (e.g. muscle, joint, other)
- date of bleeding episode
- dose (IU) and number of injections used to treat the bleed

6.5.9 Haemophilia treatment

The prescribed rFVIIIFc or rFIXFc dose (IU) and injection frequency will be collected at each follow-up visit.

Any change in haemophilia treatment (dose, injection frequency or any other change in management, for example physiotherapy) will be collected at each visit.

FVIII or FIX plasma activity levels, including dose administered (IU) and time since last dose (h) will be collected if available.

Physician judgement of patient's treatment adherence to rFVIIIFc or rFIXFc will be collected at each visit.

6.5.10 Effectiveness assessments

6.5.10.1 Ultrasound joint examination – HEAD-US

At the baseline, month 6, 12 and 18 (EOS) visits, the six index joints (elbows, knees and ankles) will be examined and scored by the investigator or delegate using the HEAD-US protocol (26). The person who performs the assessment should be properly trained and for consistency it is recommended that the same person performs the assessment at each study visit.

The HEAD-US protocol describes that a linear array 12-5 MHz US transducer is used to perform the joint examination. Elbows are examined with sweeps E1-E3 shifting the probe as described in the protocol. Knee joints planes K1-K4, and ankle joints A1-A3. There is a minor variation in the HEAD-US scoring method based on age, i.e. knee imaging scanning plane K4 is not performed in children.

One joint is scored at a time. The disease activity (synovitis) score rates the status of the hypertrophic synovium. Hypertrophic synovium is graded in three steps (0: absent/minimal; 1: mild/moderate [score=1], 2: severe [score=2]) based on the comprehensive evaluation of the joint recesses and the mean amount of synovial tissue contained in them.

The disease damage score of articular surfaces rates the structural osteochondral damage. Concerning the articular cartilage, the damage is graded in five steps (0: normal; 1: echotexture abnormalities and focal loss involving <25% of the target surface [score=1]; 2: partial/full-thickness loss of the cartilage involving at least 50% of the target surface [score=2]; 3: partial/full-thickness loss of the cartilage involving >50% of the target surface [score=3]; 4: complete cartilage destruction or absent visualization of the articular cartilage on the target surface [score=4]).

Damage of subchondral bone is scored using a three-grade scale (0: normal; 1: mild irregularities of the subchondral bone with/without initial osteophytes around the joint [score=1]; 2: deranged subchondral bone with/without erosions and presence of prominent osteophytes around the joint [score=2]).

The HEAD-US total score represents the sum of item scores for abnormalities detected and ranges from 0 up to 48.

6.5.10.2 Functional joint examination – HJHS

At the baseline and month18 (EOS) visits, the investigator or delegate will assess joint structure/function using the HJHS scoring system version 2.1 (27, 28). The person who performs the assessment should be properly trained and for consistency it is recommended that the same person performs the assessment at each study visit. The six index joints (elbows, knees and ankles) will be examined and scored. The score for each joint is the sum of the individual item scores for the 8 dimensions. Global gait is assessed separately.

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = > 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

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°

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

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 able to move through ROM gravity eliminated (gr.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 = No skills are within normal limits
NE = Non-Evaluable

The minimum score per joint is 0, the maximum score is 20.

The total joint score (range 0-120) is the sum of the 6 joint scores. The HJHS total score is total joint score + global gait (range 0-4); minimum score 0, maximum 124.

6.5.10.3 Patient-Reported Outcomes

Patient questionnaires will be administered at the baseline and 18 months (EOS), to evaluate and compare changes in patients' perceptions of pain and physical activity/function. PRO questionnaires will be completed by patients or caregivers depending on age, see Table 1 for additional details. When possible, caregivers of paediatric patients less than 8 years old will complete the PRO instruments verbatim based on the patient's responses. Patients and/or caregivers will be encouraged to complete the PROs based on the patient's age at enrolment. It is expected that it will take approximately 8-10 minutes per visit to complete all questionnaires. The PROs are expected to be completed on paper and the paper forms will be considered as the source document for the PRO data. Due to language availability, not all patients may be required to complete all PROs.

Table 1 PRO questionnaires

Instrument	Patients aged ≥6 - <12 years	Patients aged >8 - 17 years	Patients aged ≥18 years
PROMIS Pain intensity 3a			X
PROMIS Paediatric pain intensity 1a		X[2]	
PROMIS Parent proxy pain intensity 1a	X[1]		
PROMIS Pain interference short form 6a			X
PROMIS Paediatric pain interference short form 8a		X[2]	
PROMIS Parent proxy pain interference	X[1]		
PROMIS Physical function/activity short form 6b			X
PROMIS paediatric physical activity short form 8a		X[2]	
PROMIS parent proxy physical activity short form 8a	X[1]		
IPAQ-SF			X[3]

Abbreviations: IPAQ-SF: International Physical Activity Questionnaire - Short Form; PRO: patient-reported outcome; PROMIS: Patient-Reported Outcomes Measurement Information System
[1] PRO completed on behalf of the patient by the caregiver as proxy
[2] PRO completed on behalf of the patient by the caregiver, or by the patient, if possible
[3] Age range to be aligned with questionnaire age range

Information on whether questionnaires are completed by the patient or by a caregiver will be collected and accounted for in the statistical analysis.

6.5.10.3.1 PROMIS

PROMIS is a validated system of reliable and precise measures of patient-reported health status (29). The PROMIS initiative is part of the National Institute of Health (NIH) goal to develop systems to support NIH-funded research across all its institutes and centers. PROMIS measures cover physical, mental and social health and can be used for many chronic conditions. These questionnaires use a 5-point Likert response scale and a recall period of the past 7 days.

6.5.10.3.1.1 **PROMIS Pain intensity** (Pain intensity 3a (adults), paediatric pain intensity 1a, parent proxy pain intensity 1a)

Measures how much a person hurts. There are 3 questions for adults and 1/1 questions for children/parents. It takes less than a minute to complete.

6.5.10.3.1.2 **PROMIS Pain interference** (pain interference - short form 6a, paediatric pain interference short form 8a, parent proxy pain interference)

Measures consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities There are 6 questions for adults and 8/13 questions for children/parents. It takes 1-2 minutes to complete.

6.5.10.3.1.3 **PROMIS Physical function / activity** (physical function - short form 6b, paediatric physical activity -short form 8a, parent proxy physical activity short form 8a)

Includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living. There are 6 questions for adults and 8/8 questions for children/parents. It takes 1-2 minutes to complete.

6.5.10.3.2 IPAQ-SF

The IPAQ-SF is a validated, 7-day recall questionnaire suitable for people between 15-69 years of age to measure current levels of physical activity (30). IPAQ-SF assesses physical activity across domains; leisure-time physical activity, domestic and gardening activities, work-related physical activity and transport-related physical activity. The items are structured to provide separate domain specific scores for walking, moderate-intensity and vigorous-intensity activity within each of the work, transportation, domestic chores and gardening (yard) and leisure-time domains. Scoring of the IPAQ-SF results in a continuous variable in the form of total MET-minutes per week, as well as categorization into high, moderate or low physical activity level. The IPAQ-SF will be administered at baseline and at the yearly visits. It is expected to take approximately 5 minutes to complete.

6.5.11 Exploratory endpoints - florio HAEMO sub-study

If a patient has used florio HAEMO (a certified medical device used in routine clinical practice) for at least 3 months and agrees to have data collected from it by providing informed consent, the patient can participate in the florio HAEMO exploratory sub-study.

A questionnaire on the impact of florio HAEMO on patients' sense of protection and their physical activity level will be administered, and data from florio HAEMO on estimated FVIII levels, physical activity levels, bleeds, pain, well-being and rFVIIIFc/rFIXFc dosing will be collected. Data will be retrospectively collected from the 6-month period prior to enrolment, and until EOS.

6.5.11.1 florio HAEMO patient questionnaire

All patients who use florio HAEMO to monitor their haemophilia, or their caregivers for patients <12 years of age (Table 2), and who consent to the use of florio HAEMO data in the study, will

be asked to complete a questionnaire (Appendix 2 and Appendix 3) including questions about their use of florio HAEMO, and if florio HAEMO has an impact on their sense of protection and activity level. The questionnaire will be completed one time during the study and administered once a patient has used florio HAEMO for at least 3 months.

Table 2 florio HAEMO patient questionnaire

Instrument	Patients aged <8 years	Patients aged 8 to <12 years	Patients aged 12 to <18 years	Patients aged ≥18 years
florio HAEMO Patient Questionnaire	x[1, 2]	x[1, 2]	x[2]	x[2]

[1] Questionnaire completed on behalf of the patient by the caregiver as proxy
[2] Questionnaire only completed by patients that are using florio HAEMO to monitor their haemophilia

6.5.12 Safety assessments

The following safety events will be collected in this study, providing the below details have confirmed that they qualify:

- Serious Adverse Events (SAEs)
- Non-serious AEs assessed as causally related to treatment with rFVIIIFc or rFIXFc and considered unexpected
- AEs of special interest: inhibitor development, thrombotic events and serious hypersensitivity reaction including anaphylactic reactions
- AEs leading to premature discontinuation of rFVIIIFc or rFIXFc
- Exposure during pregnancy, medication errors, misuse or abuse in relation to rFVIIIFc or rFIXFc

Medication error is defined as an unintended failure in the study treatment process that leads to, or has the potential to lead to, harm to the patient; misuse is defined as situations where the study treatment is intentionally and inappropriately used not in accordance with the terms of the clinical study protocol; and abuse is defined as persistent or sporadic, intentional excessive use of study treatment by a study patient accompanied by harmful physical and/or psychological effects.

Any AE suspected to be causally related to a medicinal product other than the studied Sobi products, and which does not result from a possible interaction with it, should be reported by the Investigator to the concerned authority via the national reporting system, or to the Marketing Authorization Holder of the suspected medicinal product.

6.5.12.1 Adverse events

6.5.12.1.1 Definitions

An AE is any untoward medical occurrence in a study patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

AEs include the following:

- Abnormal test findings, as specified below
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Progression/worsening of underlying disease

In addition, signs and symptoms resulting from the following should also be handled according to the same principles as AEs:

- Overdose
- Withdrawal of treatment
- Interactions

In order to qualify for reporting as an AE in this study, at least one of the above-mentioned criteria must be met, and be in accordance with the listed safety data to be collected as defined at the beginning of this section.

For pregnancies and breastfeeding, see section 6.5.12.14.

6.5.12.2 Abnormal test findings, pre-existing conditions, procedures

Any abnormal test finding or pre-existing condition, which worsens or increases in frequency or any unplanned medical procedures should be recorded, if any of the following criteria apply:

- SAEs
- Non-serious AEs assessed as causally related to treatment with rFVIIIFc or rFIXFc and considered unexpected
- AEs of special interest: Inhibitor development, thrombotic events and serious hypersensitivity reaction including anaphylactic reactions
- AEs leading to premature discontinuation of rFVIIIFc or rFIXFc
- Exposure during pregnancy, medication errors, misuse or abuse in relation to rFVIIIFc or rFIXFc

Diagnostic and therapeutic non-invasive and planned invasive procedures, such as planned surgery, should not be reported as AEs.

6.5.12.3 Lack of efficacy

Failure of pharmacologic action or therapeutic benefit shall be recorded only when assessed as an SAE.

6.5.12.4 Serious adverse event

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death.
- Is life threatening (i.e., at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient).
- Is a medically important AE.

Medically important AEs are events that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgement, may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed 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 dependency or abuse.

Serious also includes any other event that the investigator or company judges to be serious. Any suspected transmission via a medicinal product of an infectious agent is also considered serious.

6.5.12.5 Hospitalization

Hospitalization includes transfers within a hospital (e.g. from the psychiatric unit to the intensive care unit) and also includes admissions less than 24 hours. The following situations are not considered hospitalizations (although other SAE criteria may still apply):

- Outpatient procedures/ambulatory care
- Emergency department visits

Hospitalization in the absence of an AE occurring during the study should not be considered an SAE. This includes:

- Hospitalization due to a pre-existing condition not associated with a worsening of the pre-existing condition
- Protocol-specified admission
- Elective admission, e.g. due to cosmetic surgery
- Pre-planned admission for a condition specified at baseline for the patient

6.5.12.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an adverse reaction which is not consistent with the EU SmPC.

6.5.12.7 Adverse event reporting period

The period for recording all AEs in the eCRF begins upon signature of the informed consent form and collection of non-serious AEs ends at the last study visit.

All SAEs should be reported to Sobi from the time the patient has signed the informed consent until the EOS visit. Subsequently only SAEs assessed by the investigator as related, and fatal SAEs, should be reported during the follow-up period, until EOS visit.

6.5.12.8 Obtaining and recording adverse event information

The investigator is to record all observed AEs (directly observed, spontaneously reported by the patient or solicited), in the eCRF using concise medical terminology.

Each patient will be questioned about AEs at each clinic visit following initiation of treatment. The question asked will be “Since your last clinic visit, have you had any health problems?”.

When possible and appropriate, a diagnosis rather than individual signs and symptoms shall be recorded. The investigator is responsible for obtaining sufficient information to determine seriousness, causality and outcome of each AE.

6.5.12.9 Severity assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum severity of the AE. For the purpose of consistency, these severity grades are defined as follows:

MILD	Does not interfere with patient's usual function
MODERATE	Interferes to some extent with patient's usual function
SEVERE	Interferes significantly with patient's usual function

6.5.12.9.1 Severity versus seriousness

A mild, moderate, or severe AE may or may not be serious, see section 6.5.12.4. These terms are used to describe the intensity of a specific event. Medical judgement should be used on a case-by-case basis.

For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

6.5.12.10 Causality assessment

For each AE, the investigator must make a causality assessment to determine if there is a reasonable possibility that the study treatment caused the AE. The AE is assessed as related or not related to the study treatment.

6.5.12.11 Adverse events of special interest

The following are considered adverse events of special interest:

- inhibitor development
- thrombotic events
- serious hypersensitivity reaction including anaphylactic reactions

6.5.12.12 Serious adverse event reporting

Both serious and non-serious AEs are to be reported on the AE page of the eCRF as specified in the eCRF instructions.

If an SAEs occurs, Sobi Good Pharmacovigilence Practice (GVP) will be notified by e-mail to adverseevent@sobi.com by the investigator entering the required information about the SAE into the appropriate module of the eCRF using the designated SAE form within 24 hours of awareness of the event by the investigator. This is also applicable for SAE follow-up information.

All SAEs must be recorded on the eCRF SAE form, irrespective of the study treatment received by the patient, and whether or not this event is considered by the investigator to be related to study treatment. The investigator must complete the eCRF SAE form in English and must assess the causal relationship of the event to study treatment.

The eCRF SAE collection form is not the same as the AE eCRF form. The forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

If the eCRF is not functioning, the SAE can be reported by emailing a completed paper SAE report form, using the e-mail address adverseevent@sobi.com. The event must be updated electronically in the eCRF by the clinical site once eCRF function resumes.

All new information obtained, relevant to an SAE report, should be forwarded to Sobi GVP by e-mail to adverseevent@sobi.com within the same timeframe as the initial information.

The investigator shall provide Sobi GVP with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide Sobi with additional information related to any SAE as requested.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Sobi/CRO, will review it and will notify the IECs, if appropriate according to local requirements.

Sobi Global pharmacovigilance & patient safety (GPV)will report SUSARs to the relevant Health Authorities in all concerned countries according to local regulations. Sobi/CRO will notify central IECs according to local requirements, and investigators.

6.5.12.13 Follow-up of unresolved adverse events

All reported AEs should be followed up until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends, i.e., until the last scheduled

visit. How to report changes in an ongoing AE during a patient's participation in the study is described in the eCRF instructions.

In addition, all serious and non-serious AEs assessed by the investigator as related to the study treatment should continue to be followed up until they resolve or until the investigator assesses them as “chronic” or “stable”, even after the patient's participation in the study is over, but without further recordings into the eCRF.

6.5.12.14 Exposure during pregnancy and breastfeeding

All events of exposure to the study treatment during pregnancy (female patient or male patient’s partner) or breastfeeding, shall be reported to Sobi GPV by e-mail to adverseevent@sobi.com within 24 hours of awareness by any study personnel using the Pregnancy Notification Form, whether the exposure is associated with an AE or not. This includes all situations where a female is or has been found to be pregnant after being exposed to study treatment; directly, indirectly or via her partner (paternal exposure).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy Report Form which shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi of relevant information and any information requested related to the outcome of the pregnancy.

Before collecting any details on the pregnancy, its outcome, the birth, and health of the baby, a separate consent form should be collected from the mother and/or the father of the child, as required by local regulations.

Any AEs and SAEs observed during and in relation to pregnancy, delivery or breastfeeding should be recorded in the eCRF and, as applicable, be reported to Sobi as described previously in this section.

6.5.12.15 Appropriateness of safety measurements

The safety measurements in this study is in line with the scope and type of the clinical study, the level of knowledge on the safety profile of the study drugs, the disease profile of the study patients, and supported by EU regulatory requirements.

7 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, Sobi and/or CRO SOPs, the ICH GCP Guideline (2), and applicable regulatory requirements.

The sponsor will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data which would affect patient safety and reliability of study data.

The Sponsor will establish a systematic, prioritized, risk-based approach to monitoring and has chosen a combination of on-site and centralized monitoring.

Monitoring visits to the study site will be performed periodically during the study, to help ensure compliance with the protocol, study specific procedures and applicable regulatory requirements. Source documents will be reviewed for verification of agreement with data in CRFs. All patient informed consent forms will be reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be patient to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

8 Statistical plan

8.1 Determination of sample size

With a sample size of 250 patients (200 with haemophilia A and 50 with haemophilia B) assuming a standard deviation of 13, the mean change from baseline in Total HEAD-US score will be estimated with a level of accuracy that is lower than a clinically meaningful worsening of 2, e.g. a half width of 1.61 (Table 3). The standard deviation is based on the expected variability among the patients with regards to prior treatment before enrolment and the diversity of joint status.

Table 3 Determination of sample size

Confidence level	Standard deviation	n	Half width
95%	7	250	0.87
95%	10	250	1.25
95%	13	250	1.61
95%	13	200	1.80

8.2 Definition of study populations

Full analysis set (FAS): All patients enrolled in the study.

Per protocol (PP) analysis set: All patients enrolled in the study who completed the study without any major protocol violations.

8.3 Overall statistical and analytical plan

8.3.1 General statistical issues

A detailed Statistical Analysis Plan (SAP) describing further details of the statistical analyses to be used will be prepared prior to first patient in.

All continuous variables will be summarized with descriptive statistics including number of observations, mean, standard deviation, median, quartiles, minimum and maximum values. Categorical variables will be summarized in frequency tables including number of observed responses in each category as well as percentages. Number of missing observations will also be displayed. No formal statistical hypothesis testing is planned.

Baseline is defined as the measurements taken on Visit 1.

Historical data (6-months before enrolment) will be tabulated by type of haemophilia, total and listed.

8.3.2 Demographics and baseline characteristics

All demographics and baseline characteristics will be summarized with descriptive statistics by type of haemophilia and in total. Individual patient data will be listed.

Disposition: Patient disposition will be listed with any withdrawals flagged. Frequencies (number and %) of the total number of patients enrolled, completed, prematurely withdrawn (including reason for withdrawal) from the study, number of sites with at least one patient enrolled, number of patients in the FAS and number of patients in the PP set will be summarized.

Demographics: Demographic data (age, weight, height, severity of haemophilia and type of haemophilia (A or B)) at baseline visit will be summarized and listed by descriptive statistics.

Number and location of impaired joints at baseline will be presented by descriptive statistics.

8.3.3 Analysis related to primary objective

The primary objective is to evaluate the overall joint status as detected by US in haemophilia A and B patients treated with rFVIIIFc or rFIXFc prophylaxis over the 18-month study period.

The primary endpoint is change from baseline in total HEAD-US score up to month 18 (EOS) and will be based on both the FAS and PP set.

The primary endpoint, change from baseline, will be calculated from baseline (Visit 1) to month 18 (EOS). The change in HEAD-US score will also be calculated from baseline to month 6 and month 12. Mean change from baseline for the primary endpoint, will be estimated using a generalized linear mixed model for repeated measures, adjusted for clinically important covariates (for example, age, severity of haemophilia, type of haemophilia, presence of joint disease at inclusion, prophylactic regimen and dose intensity) as applicable. The estimated mean

change from baseline in Total HEAD-US score will be presented with 95% confidence interval. In general, patients with events that could affect the interpretation of the Total HEAD-US score but not leading to discontinuation of treatment will be included in the primary analysis. Patients with events leading to discontinuation of treatment will be included in the primary analysis including all data collected up to discontinuation. To assess the robustness of these results, sensitivity analyses will be performed including one based on the PP analysis set. Further details will be specified in the SAP.

Examples of subgroups that will be created if applicable, to further explore the endpoint are age (6-<12, 12-<18, ≥18 years), severity of haemophilia (mild/moderate/severe), type of haemophilia (A/B), presence of joint disease at inclusion (synovial hypertrophy and/or osteochondral changes), prophylactic regimen (primary/secondary/tertiary), dose intensity cross tabulated by change vs. no change in HEAD-US score, treatment (on demand vs. prophylaxis) prior to enrolment into the study and compliance (if e.g. 20% of the patients have < 80% compliance).

If there are few mild and moderate patients then these two severities will be pooled.

The HEAD-US score represents the sum of item scores for abnormalities detected. Its values range from 0 (minimum) to 8 (maximum), see Table 4.

Table 4 HEAD-US scoring method

Disease activity (synovitis)	Scale
Hypertrophic synovium	
Absent/Minimal	0
Mild/Moderate	1
Severe	2
Disease damage (articular surfaces)	
Normal	0
Echotexture abnormalities, focal partial/full-thickness loss of the articular cartilage involving <25% of the target surface	1
Partial/full-thickness loss of the articular cartilage involving at least ≤50% of the target surface*	2
Partial/full-thickness loss of the articular cartilage involving >50% of the target surface	3
Complete cartilage destruction or absent visualization of the articular cartilage on the target bony surface	4
Bone	
Normal	0
Mild irregularities of the subchondral bone with/without initial osteophytes around the joint	1
Deranged subcondral bone with/without erosions and presence of prominent osteophytes around the joint	2
Note: Elbow: anterior aspect of the distal humeral epiphysis, Knee: femoral trochlea; Ankle: anterior aspect of the talar dome.	

8.3.4 Analysis related to secondary objectives

A detailed description of the secondary objectives and endpoints are found in section 5.2 of the protocol. The secondary endpoints will be based on both the FAS and the PP set.

HEAD-US scores (hypertrophic synovium, cartilage, bone) and HJHS scores (Sum of joint totals, Global Gait Score, HJHS total score) will be presented using descriptive statistics at each visit. In addition, the change from baseline to each post-baseline visit will also be presented with descriptive statistics and the estimated average change from baseline together with 95% CI.

The number and proportion of patients with target joints as well as the total number of target joints will be analyzed by summary statistics as well as frequency tables for each visit. Target joint locations will be given for each visit in frequency tables.

The ABR for treated bleeds and ABR for all (treated and untreated bleeds) will be derived for the period between baseline and month 6 visit, for the period between month 6 and month 12 visit, for the period between month 12 and month 18, and as well as for the entire 18-month study period. The ABR will also be presented for the retrospective 6 month period. ABR will be presented using summary statistics for all periods and also be presented by type (spontaneous/traumatic/unknown) and location (joint/muscle/unknown). The number and

percentage of patients who had a at least one bleeding episode (overall, circumstance, locations and target joint) over the 18-month prospective period will also be presented as well as the corresponding total number of episodes. The number and proportion of patients with 0 joint bleeds will be presented, as well as the number and proportions with 1, 2 etc. joint bleeds. To justify an estimation of the ABR and to reduce potential misclassification, a patient had to be documented for at least 3 months.

PROMIS and IPAQ-SF scores will be presented at baseline and 18 months graphically and in tabular form with descriptive statistics (mean IPAQ-SF score measured as MET-minutes/week) and change.

8.3.5 Analysis related to exploratory objectives

All patients who use florio HAEMO or their caregivers for patients <12 years of age and who consent to the use of florio HAEMO data in the study, will, once they have used florio HAEMO for at least 3 months, be asked to complete a questionnaire with questions about their use of florio HAEMO, how it affects their haemophilia management, and if it has an impact on their sense of protection and activity level. The results from the questionnaire will be summarized using descriptive statistics as appropriate. Data generated from florio HAEMO (treatment adherence scores, estimated FVIII or FIX levels, physical activity levels, dosing, bleeds, pain, well-being) will be analyzed and described in the SAP.

8.3.6 Analysis of safety and tolerability data

8.3.6.1 Adverse events

Reported AEs during the study will be coded using the Medical Dictionary for Regulatory Activities. The incidence of AEs will be summarized in frequency tables by treatment, system organ class, preferred term and maximum severity. Separate tabulations will performed for serious and non-serious AEs.

8.3.7 Interim analysis

Interim analyses are planned to be performed during the study. The first interim analysis is to be performed once recruitment is completed. The purpose of the first interim analysis is to assess the baseline variability of HEAD-US results and to share baseline characteristics with the haemophilia community. The second interim analysis is planned to be performed once at least 50% of the patients have completed their 12-month visit and will evaluate the joint health status at that time.

8.3.8 Handling of missing data

Methods for handling missing data will be described in the SAP.

9 Data collection, handling and record keeping

9.1 Data standards

Collection of data should be performed in the Clinical data acquisition standards harmonization format, according to the Clinical data interchange standards consortium (CDISC). The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as 'Required' in the Study Data Tabulation Model format.

9.2 Case report form

A CRF is required and should be completed for each enrolled patient. In this study a web based, validated electronic data capture (EDC) software tool will be used to collect and process the study data. The management of the EDC system will be based on the model of outsourcing.

The data should be entered by site users into the EDC system on an ongoing basis. In principle, it is recommended to perform data entry within 5 working days from the visit date unless otherwise specified by the site Clinical Trial Agreement. To ensure data quality within EDC, automated edit checks will be built into the EDC system and triggered to correct or verify the input data. Any data changes or modifications within EDC will be automatically tracked by an audit trail detailing date, time and name of the user performing corrections.

Clinical data management will be conducted in accordance with regulatory standards. This applies to data recorded directly in eCRF and to data from other sources stored at secure servers (e.g. IXRS, Laboratory). Additional details regarding data collection and validation procedures will be detailed in a Data Management Plan.

Access to the EDC system is granted and revoked in accordance with regulatory requirements. Only authorized personnel will have access to the EDC system upon completion of the user training.

The investigator will review and approve the eCRF entries for each patient with an electronic signature. The signatures serve to attest that the information contained on the eCRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all data entered in the eCRF.

The completed original eCRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Sobi.

At the end of the study, a final copy of the database will be stored at the Sponsor. Sobi will ensure that an eCRF copy of trial's final and locked data is provided to the Investigator in a form of a write protected PDF files and that the eCRF copies are an exact copy of the data maintained in the database.

9.3 Source data

Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In those cases, the information collected in the eCRFs must match those charts. In some cases, a portion of the source documents for a given patient may be the eCRF.

The florio HAEMO database will be considered as the source for the florio HAEMO data.

A separate source document location agreement will be completed and signed by the principal investigator and the monitor before study start.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trial).

9.4 Protocol deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purpose of this protocol, deviations requiring notification to CRO are defined as any patients who:

- Entered into the study even though they did not satisfy entry criteria;
- Developed withdrawal criteria during the study and were not withdrawn;

When a deviation from the protocol is identified, the investigator or designee must ensure the CRO is notified. The CRO will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or effectiveness of the patient to determine patient continuation in the study.

The investigator and CRO must contact Sobi immediately if a deviation is discovered that significantly affects or has the potential to significantly affect human patient protection or the reliability of study results.

The investigator will also assure that deviations are reported and documented in accordance with IEC and applicable regulatory requirements.

9.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before breaking of the blind and before generation of any results. The database lock will be approved by relevant study personnel and all edit accesses will be removed.

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before generation of any results. The database lock will be approved by relevant study personnel and all edit accesses will be removed.

If data errors are detected after database lock which either:

a) Have a significant impact on the statistical outcome of the analysis

b) Affects the safety profile of the investigational product

c) Affects the benefit-risk of the investigational product

the database may be unlocked if approved.

9.6 Record retention

The investigator should maintain a record of the location(s) of investigator's essential documents as defined in the ICH GCP Guideline (2) including source documents and should have control of and continuous access to all essential documents and records generated by the investigator/institution before, during, and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi or Sobi's representatives.

When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfill the requirements for certified copy as defined in ICH GCP Guideline (2).

The records of the clinical trial should be retained by the Investigator for at least 25 years after the end of the clinical trial. However the medical files of patients shall be archived in accordance with national law. Further details around archiving is specified in the Clinical Trial Agreement.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution.

9.7 Data protection

Study patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IECmembers, and by inspectors from regulatory authorities.

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10 End of study

The end of this study is defined as the date of last patient out, i.e., the last patient's last visit.

11 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients before the next scheduled site visit. All study materials must be collected and all the CRFs completed to the greatest extent possible.

12 Dissemination and publication of results

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on www.clinicaltrials.gov and EudraCT. The results of this study will be published within 6 months of the EOS.

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent and Stimely manner. Sobi follows the principles of the International Committee of Medical Journal Editors recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship (31).

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

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Appendix 1 Study Administrative Structure

Monitoring: IQVIA Ltd., Reading, United Kingdom

SAE reporting: Shared responsibility between IQVIA Ltd., Reading, United Kingdom and Swedish Orphan Biovitrum AB (publ), Stockholm, Sweden

Data management: IQVIA Ltd., Reading, United Kingdom

Statistics: IQVIA Ltd., Reading, United Kingdom

Appendix 2 florio HAEMO Patient Questionnaire

florio HAEMO Effect on Sense of Protection & Activity Level

Have you used any other haemophilia management tool before?

- o Yes
- o No

If yes; enter the one(s) you have you used: _____

How often did you use florio HAEMO to monitor your estimated FVIII or FIX levels in the last month?

- o Daily
- o A few times per week
- o Once weekly
- o A few times per month
- o Never

Since you started using florio HAEMO, do you feel more in control of your haemophilia?

- o In much better control
- o In better control
- o No difference
- o In worse control
- o In much worse control

Since you started using florio HAEMO, do you feel more protected against bleeds?

- o Much more protected
- o More protected
- o No difference
- o Less protected
- o Much less protected

Has florio HAEMO helped you in choosing the timing of your physical activities?

- o Yes
- o No

Has florio HAEMO helped you to facilitate care planning and potential treatment adjustment discussions with your health care provider?

- o Yes
- o No

Would you recommend the use of florio HAEMO to other haemophilia patients?

- o Yes
- o No

If you answered no, can you comment on the reason(s)?

_____

Patient Study ID: _____

Date of completion: _____

Version 1.0 Final 15 November 2022

Appendix 3 florio HAEMO Caregiver Questionnaire

florio HAEMO Effect on Sense of Protection & Activity Level

Has your child used any other haemophilia management tool before?

- o Yes
- o No

If yes; enter the one(s) you have you used: _____

How often did your child use florio HAEMO to monitor his/her estimated FVIII or FIX levels in the last month?

- o Daily
- o A few times per week
- o Once weekly
- o A few times per month
- o Never

Since your child started using florio HAEMO, do you feel more in control of your child's haemophilia?

- o In much better control
- o In better control
- o No difference
- o In worse control
- o In much worse control

Since your child started using florio HAEMO, do you feel that your child is more protected against bleeds?

- o Much more protected
- o More protected
- o No difference
- o Less protected
- o Much less protected

Has florio HAEMO helped your child in choosing the timing of his/her physical activities?

- o Yes
- o No

Has florio HAEMO helped you and your child to facilitate care planning and potential treatment adjustment discussions with his/her health care provider?

- o Yes
- o No

Would you recommend the use of florio HAEMO to other haemophilia patients?

- o Yes
- o No

If you answered no, can you comment on the reason(s)?

_____

Patient Study ID: _____

Date of completion: _____

Version 1.0 Final 15 November 2022

Signature Page

Name: DS-2022-024-7943
Title: Sobi.HAEM89-007 CSP v1.0 FINAL 15Nov2022
Version: 1.0,CURRENT

Signed by:	PPD
Signed date:	2022-11-16 09:28:57
Role / Intention	Author Approval

Signed by:	PPD
Signed date:	2022-11-16 09:29:24
Role / Intention	Project Manager Approval

Signed by:	PPD
Signed date:	2022-11-16 09:34:26
Role / Intention	Author Approval

Signed by:	PPD
Signed date:	2022-11-16 19:25:01
Role / Intention	Medical Approval

Signed by:	PPD
Signed date:	2022-11-17 08:44:42
Role / Intention	SME Approval