total weight-adjusted consumption of BPAs

- To evaluate the effects of fitusiran as compared to on-demand treatment with BPAs on joint status
- To evaluate the effects of fitusiran as compared to on-demand treatment with BPAs on patient resource use.

**Endpoints**

**Primary**

- Annualized Bleeding Rate (ABR) in the efficacy period

**Secondary**

- ABR in the treatment period
- Annualized spontaneous bleeding rate in the efficacy period
- Annualized joint bleeding rate in the efficacy period
- Change in Hemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) physical health score and total score in the treatment period
- ABR in the onset period

**Exploratory**

- Change in the following in the treatment period:
  - Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores
  - Hemophilia Activities List (HAL) scores
  - Pediatric HAL (pedHAL) scores
  - EuroQol-5 dimension (EQ-5D) scores
  - Hemophilia Quality of Life Questionnaire for children and adolescents (Haemo-QOL) scores
  - Hemophilia Joint Health Score (HJHS)
- Number of target joint bleeding episodes
- Incidence and titer of antidrug antibodies to fitusiran in the fitusiran treatment arm
- Antithrombin (AT) activity level over time
- Thrombin generation over time
- Fitusiran plasma levels
- Annualized weight-adjusted consumption of BPAs
- Change in patient resource use (eg, work/school attendance, visits to doctor/hospital)

**Safety**

- Incidence, severity, seriousness, and relatedness of adverse events (AEs)

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ET | Early termination |
| FIX | Factor IX |
| FV | Factor V |
| FVII | Factor VII |
| FVIII | Factor VIII |
| FX | Factor X |
| GalNAc | N-acetylgalactosamine |
| GCP | Good Clinical Practice |
| GGT | Gamma glutamyl transferase |
| GLP | Good Laboratory Practice |
| HAL | Hemophilia Activities List |
| Haem-A-QOL | Hemophilia Quality of Life Questionnaire for Adults |
| Haemo-QOL | Hemophilia Quality of Life Questionnaire for children and adolescents |
| HBc Ab | Hepatitis B core antibody |
| HBs Ag | Hepatitis B surface antigen |
| HIV | Human immunodeficiency virus |
| HRQOL | Health-related quality of life |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |
| IP | Investigational product |
| IRB | Institutional Review Board |
| IRS | Interactive response system |
| ISR | Injection site reaction |
| ITT | Intent-to-treat |
| ISTH | International Society on Thrombosis and Hemostasis |
| ITI | Immune tolerance induction |
| IV | Intravenous |
| LFT | Liver function test |

Quality of Life Questionnaire for Adults (Haem-A-QOL) physical health score and total score in patients ≥17 years of age, ABR in the onset period, and the overall safety profile.

Characterization of bleeding episodes is clinically relevant to assess overall bleeding episode protection. Joint bleeding episodes result in pain and hemarthrosis, leading to progressive joint destruction, and hence are important to assess. The Haem A-QOL is a hemophilia-specific HRQOL survey instrument that has been validated in other hemophilia clinical trials and is considered the most appropriate HRQOL tool for this study.

The study population will be comprised of males ≥12 years of age; it is appropriate to study fitusiran in adolescents (patients ≥12 to <18 years of age) because the pathophysiology of disease progression and bleeding episode management is the same as adults and self-management of hemophilia typically begins at 12 years of age.[6] A similar study in hemophilia patients without inhibitors (ALN-AT3SC-004 [EFC14769]) is being conducted concurrently to this study.

To protect against bias, patients will be assigned to fitusiran (fitusiran treatment arm; N=36) or on-demand BPA therapy (on-demand arm; N=18) by stratified randomization.

The onset period duration reflects modeling data that estimates it takes approximately 28 days to reach the therapeutic target range in the majority of patients. Efficacy of fitusiran will be assessed over the remaining 8 months of the study (Day 29 to Month 9).

In the event of a breakthrough bleeding episode, on-demand use of BPAs will be permitted throughout the entire study duration (see Section 6.3.1).

## 1.4. Dose Rationale

Dose selection was guided by the principle of identifying an optimal dose that is both well-tolerated and efficacious. The fitusiran dose proposed for Phase 3 development was identified based on observed data from ongoing clinical studies, as well as extensive clinical simulations and modeling. The key PD and clinical parameters used to support the dose selection include decreases in AT activity, the most proximate and direct PD effect of fitusiran, as well as increases in thrombin generation and decreases in ABR.

Observed data from Phase 1 and Phase 1/2 studies in patients with hemophilia A and B, with or without inhibitors, and PK/PD modeled data, support selection of a fixed dose of 80 mg for this study, as subcutaneously administered once-monthly.

In observed data from Phase 1 and Phase 1/2 studies, monthly equivalent doses or monthly doses ranging from 0.045 mg/kg to 1.8 mg/kg and fixed doses of 50 mg and 80 mg have been evaluated. A clear dose response trend of increased AT lowering is evident, with approximately 10% to 20% residual AT activity at a dose of 1.8 mg/kg and at fixed doses of 50 mg and 80 mg subcutaneously administered once monthly. These data suggest that the maximum AT lowering achieved as a function of the dose administered reaches an asymptote at ~90% AT lowering and that it is unlikely higher doses will achieve meaningfully greater AT lowering. In addition, both the 50 mg and 80 mg fixed doses produced substantial increases in peak thrombin generation, which approach the lower end of the normal range, but do not exceed the normal range.

Dose-response modeling analyses are supportive of the observed data. A repeated time to event model was used to evaluate the relationship between AT lowering and the anticipated ABR. According to the model, the 80 mg, fixed, once-monthly dose is anticipated to result in near

## 2.2. Secondary Objectives

- To evaluate the efficacy of fitusiran compared to on-demand treatment with BPAs, as determined by:
  - The frequency of spontaneous bleeding episodes
  - The frequency of joint bleeding episodes
  - Health-related quality of life (HRQOL) in patients ≥17 years of age
- To determine the frequency of bleeding episodes during the onset period
- To determine the safety and tolerability of fitusiran

## 2.3. Exploratory Objectives

- To evaluate the effects of fitusiran as compared to on-demand treatment with BPAs on the following patient-reported outcomes:
  - Patient satisfaction with treatment
  - Patient activity
  - HRQOL in adolescents (≥12 to <17 years of age)
- To determine the pharmacodynamic (PD) effect, pharmacokinetics (PK), and immunogenicity of fitusiran
- To evaluate the effects of fitusiran as compared to on-demand treatment with BPAs on the total weight-adjusted consumption of BPAs
- To evaluate the effects of fitusiran as compared to on-demand treatment with BPAs on joint status
- To evaluate the effects of fitusiran as compared to on-demand treatment with BPAs on patient resource use

# 3. ENDPOINTS

## 3.1. Primary Endpoint

- Annualized Bleeding Rate (ABR) in the efficacy period

## 3.2. Secondary Endpoints

- ABR in the treatment period
- Annualized spontaneous bleeding rate in the efficacy period
- Annualized joint bleeding rate in the efficacy period
- Change in Haem-A-QOL physical health score and total score in the treatment period
- ABR in the onset period

## 3.3. Exploratory Endpoints

- Change in the following in the treatment period:
  - Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores
  - Hemophilia Activities List (HAL) score
  - Pediatric HAL (pedHAL) score
  - EuroQol-5 dimension (EQ-5D) score
  - Hemophilia Quality of Life Questionnaire for children and adolescents (Haemo-QOL) score
  - Hemophilia Joint Health Score (HJHS)
- Number of target joint bleeding episodes
- Incidence and titer of antidrug antibodies to fitusiran in the fitusiran treatment arm
- AT activity level over time
- Thrombin generation over time
- Fitusiran plasma levels
- Annualized weight-adjusted consumption of BPAs
- Change in patient resource use (eg, work/school attendance, visits to doctor/hospital)

## 3.4. Safety Endpoint

- Incidence, severity, seriousness, and relatedness of adverse events (AEs)

# 4. INVESTIGATIONAL PLAN

## 4.1. Summary of Study Design

The ATLAS-INH trial (ALN-AT3SC-003) is a multicenter, multinational, randomized, open-label Phase 3 study designed to evaluate the efficacy and safety of fitusiran in male patients aged ≥12 years with hemophilia A or B, with inhibitory antibodies to FVIII or FIX, who are not receiving prophylactic therapy.

The study will be conducted at approximately 100 clinical study centers worldwide.

Eligible patients will be randomized in a 2:1 ratio to:

- **Fitusiran treatment arm**: Fitusiran 80 mg administered SC as prophylaxis once monthly, with use of on-demand BPA for treatment of breakthrough bleeding episodes
- **On-demand arm**: On-demand BPA for treatment of breakthrough bleeding episodes

On-demand use of BPAs is defined as the use of these agents, as needed, for episodic bleeding episodes, and not on a regular regimen intended to prevent spontaneous bleeding. Throughout

the study, patients in the fitusiran treatment arm may receive on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate. For patients in the fitusiran treatment arm who have received at least 1 dose of fitusiran and are being treated for breakthrough bleeding episodes, it is recommended to follow the guidelines provided in Section 6.3.1 per Investigator discretion.

Bleeding events and doses of BPA administered during the conduct of the study will be recorded in an electronic Diary (eDiary) as described in Section 7.2.1. Since bleeding episodes are recorded as an efficacy assessment of fitusiran, these will not be treated as AEs unless they meet any of the SAE criteria listed in Section 7.5.6.1. Safety, quality of life, pharmacodynamic, and pharmacokinetic data will also be collected.

All patients will be treated for a total of 9 months; patients randomized to the fitusiran treatment arm will receive a total of 9 SC injections of fitusiran. Because the full PD effect of fitusiran is not achieved until approximately 28 days after receiving the first dose, efficacy will be assessed during the final 8 months on study (Day 29 to Month 9). Therefore, the overall fitusiran treatment period is defined as the onset period (Day 1 to Day 28 after receipt of the first dose, during which the AT lowering capacity of fitusiran is increasing but has not yet reached therapeutic levels) plus the efficacy period (Day 29 and after, when the AT lowering capacity of fitusiran has achieved therapeutic target range).

Patients may undergo unplanned or emergency surgery during the study, but must not schedule non-urgent surgery to occur during the study. Perioperative guidance should be followed as specified in Section 6.6.

A Study Steering Committee, composed of experts in the field of hemophilia, will advise the Sponsor on study design and conduct (Section 4.6).

An independent data monitoring committee (DMC) will oversee the safety and overall conduct of this study as described in Section 4.7.

The study design schema is presented in Figure 1. Patients who complete the study may be eligible for an open-label extension study in which patients coming from both the fitusiran and on-demand arms will be administered monthly SC doses of fitusiran.

## 6.6. Elective and/or Emergency Surgery

If an urgent need for surgery arises during the study period, the study Medical Monitor will be informed and the perioperative hemostatic treatment plan will be communicated to the study Medical Monitor unless clinical circumstances do not allow.

It is recommended that, when possible, any elective non-dental major surgery be performed at a clinical study center.

For reference, see Appendix (Section 11.2.1) for definitions of minor and major surgery.

***Perioperative Treatment Plan***

In patients in both the on-demand and fitusiran treatment arms undergoing surgery, a written perioperative treatment plan will be reviewed with the study Medical Monitor before conducting the procedure, unless clinical circumstances do not allow. In patients on fitusiran, the perioperative treatment plan should be developed using the same principles as bleed management described in Section 6.3.1 and the guideline below:

- If the clinical circumstance is such that the recommended doses and/or dose intervals in Table 4 are deemed insufficient for hemostasis, consider AT replacement and manage thrombotic risk as per Investigator practice for a hemophilia patient undergoing that particular surgery.
- Non-pharmacologic methods of thromboprophylaxis should also be employed as clinically indicated.

***Fitusiran Treatment During the Perioperative Evaluation Period***

For reference, see Appendix (Section 11.2.1) for definitions of minor and major surgery.

If the need for a major surgery arises during the trial and the procedure is not an emergency or urgent, it is recommended that the procedure be postponed until after completion of the trial.

For minor operative procedures, dosing with fitusiran may continue uninterrupted.

If the need for emergency or urgent major surgery arises during the trial, the patient should be managed medically according to the guidelines above. If a fitusiran dose is scheduled to occur on or in close proximity to the day of surgery, or anytime during the perioperative period, the dose should be withheld. The Perioperative Evaluation Period is defined as the day of the surgery through the final day on which supplemental hemostatic or antithrombotic treatments are administered as part of the perioperative treatment plan. Fitusiran dosing may be resumed at the next scheduled visit following the Perioperative Evaluation Period at the discretion of the Investigator. If multiple consecutive doses of fitusiran are withheld, the Investigator will consult with the study Medical Monitor, who will determine if the patient may continue on study.

Perioperative assessments will be performed in patients undergoing surgery during the study as described in Appendix Section 11.2.2 and as scheduled in Table 10.

## 6.7. Management of Sepsis

Formal clinical guidelines do not currently recommend correction of low AT that is seen in the setting of sepsis, citing a lack of evidence for improved outcomes and an increased risk of

### 7.1.1. Patient Education Module

Patients will be educated by Investigators or trained healthcare professionals on coagulation and general considerations with regard to managing hemophilia in the clinical setting of lowered-AT. This will be performed as specified in the Schedule of Assessments (Table 1).

### 7.1.2. Inhibitor Status

Patients inhibitor status will be determined as specified in the Schedule of Assessments (Table 1) by Nijmegen modified Bethesda assay.

### 7.1.3. FibroScan or FibroTest/APRI

A FibroScan or FibroTest/APRI will be performed according to the Schedule of Assessments (Table 1) to rule out cirrhosis in patients with a history of Hepatitis C.

## 7.2. Efficacy Assessments

***Bleeding Episode Definitions***

A bleeding episode is defined as any occurrence of hemorrhage that requires administration of factor concentrates or BPA infusion, eg, hemarthrosis, muscle, or mucosal bleeding. Since bleeding episodes are recorded as an efficacy assessment of fitusiran, these will not be treated as AEs unless they meet any of the SAE criteria listed in Section 7.5.6.1.

The definition of bleeding episode types described below is based on consensus opinion of International Society on Thrombosis and Haemostasis (ISTH) as reflected in a recent publication.[12]

The start time of a bleeding episode will be considered the time at which symptoms of a bleeding episode first develop. Bleeding or any symptoms of bleeding at the same location that occurs within 72 hours of the last injection used to treat a bleeding episode at that location will be considered a part of the original bleeding event, and will count as one bleeding episode towards the ABR. Any bleeding symptoms that begin more than 72 hours from the last injection used to treat a bleeding episode at that location will constitute a new bleeding event.

A spontaneous bleeding episode is a bleeding event that occurs for no apparent or known reason, particularly into the joints, muscles, and soft tissues.

A joint bleeding episode is characterized by an unusual sensation in the joint (“aura”) in combination with 1) increasing swelling or warmth over the skin over the joint, 2) increasing pain, or 3) progressive loss of range of motion or difficulty in using the limb as compared with baseline.

A muscle bleed may be characterized by pain, swelling and loss of movement over the affected muscle group.

A target joint is defined as a joint where 3 or more spontaneous bleeding episodes in a single joint within a consecutive 6-month period has occurred; where there have been ≤2 bleeding episodes in the joint within a consecutive 12-month period the joint is no longer considered a target joint.

A traumatic bleeding episode is one that is caused by a known injury or trauma. Bleeding episodes sustained during sports and recreation will be counted as traumatic bleeding episodes, but patients will be asked to indicate in the eDiary that the event occurred during such activities. Training will be provided on this and other aspects of eDiary use (see Section 7.2.1).

Annualized bleeding rate will be calculated as described in Section 8.2.5.1. Bleeding episodes will be managed according to Section 6.3.1.

### 7.2.1. Electronic Diary

Patients will be issued an eDiary to record all bleeding events and all doses of BPAs administered during the conduct of the study. Entries are to be made in a timely manner, and it is preferred that doses are entered immediately upon administration or within 24 hours. Patients will be prompted to enter bleeding location, severity, causality (spontaneous or traumatic), doses of bypass agents, and reasons for dosing (prophylaxis, treatment of a bleed, and preventive dose for anticipated activity). Training of patients should be documented in the appropriate source record.

The Sponsor or an independent delegate will review diary entries for data quality to identify issues such as subjects who may need retraining on diary use and timely entry of bleeding episode information.

Bleeding episodes will be recorded by the patient in the eDiary, and reviewed by the Investigator (and Sponsor or independent delegate) continuously for the study duration. The site will contact the patient at a minimum interval of every 2 weeks per schedule of assessments to review diary records and ensure that the patient is utilizing the device appropriately.

Sites will be notified when patients enter initial treatments for bleeding events into their eDiaries. If the dose amount exceeds the recommended dose according to the bleeding episode management plan, the patient must be contacted as soon as possible, preferably within 24-48 hours of receiving the alert. At the time of contact the patient's clinical condition will be reviewed along with the dose and efficacy of the treatment given, and the Investigator will provide appropriate guidance regarding further management of the bleeding episode. The site will also receive an alert, and must make contact with the patient as soon as possible if a third dose of product is administered for a single bleed, to review clinical condition, the need for further therapy, and appropriate ongoing management of the bleeding episode required to achieve hemostasis.

In addition, patients will be instructed to contact the site if they feel they need to administer BPA at a higher dose level or higher frequency than their bleeding episode management plan recommends, or if more than two doses are required to achieve hemostasis.

Complete instructions will be provided in the Study Manual.

## 7.3. Pharmacodynamic Assessments

In this study, AT activity level and thrombin generation will be collected as measurements of PD effect. These measurements will be collected and analyzed centrally for research purposes. As interpretation is uncertain, thrombin generation results will not be used to adjust dosing of fitusiran or guide other elements of study conduct or clinical management and will not be shared

with sites until after study completion. If clinical circumstances arise for which AT activity levels are required to guide patient care, local laboratory assessments may be drawn.

### 7.3.1. Antithrombin (AT) Activity

AT activity level will be assessed according to the schedule of assessments (Table 1); samples will be collected within 4 hours prior to dosing. Antithrombin levels will be determined by validated assay. Antithrombin protein may be measured in a subset of plasma samples for correlation. Results will be collected and interpreted centrally.

In the fitusiran treatment arm patients who do not enroll in the extension study, following final fitusiran dose, AT activity level will be monitored at monthly intervals until returning to an activity level of approximately 60% (per the central laboratory) or per Investigator discretion in consultation with the study Medical Monitor.

### 7.3.2. Thrombin Generation

Thrombin generation will be assessed according to the Schedule of Assessments (Table 1) using a functional assay per the Laboratory Manual, and will be collected and interpreted centrally.

### 7.3.3. Exploratory Analyses

Except where prohibited by local or national regulations, in consented patients, plasma, serum, and urine samples may be archived and used for analyses of exploratory biomarkers related to the metabolic profiling or effects of fitusiran and for the development of modified thrombin generation assays, and may also be archived for use in other exploratory analyses related to hemophilia and its complications.

In addition, where permitted in consented patients, serum samples may be used for analysis of circulating RNA, including the assessment of cleaved AT RNA, and a sample of DNA may be obtained and archived to permit potential confirmation of hemophilia mutation or genotyping of hemophilia modifier genes or genes that may modify the effects of fitusiran.

## 7.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of PK including metabolites (as necessary) in all fitusiran arm patients according to the collection schedule presented in Table 7, on the days specified in the Schedule of Assessments (Table 1).

Blood must be aliquoted and processed as plasma for PK analysis. All plasma concentration data (Table 7 and Table 8) will be summarized and analyzed using a population PK approach.

In addition, plasma PK (Table 8, which includes all time points in Table 7) will be evaluated in East Asian patients in the fitusiran arm at East Asian sites (defined as patients from sites in China, Japan, South Korea, and Taiwan), and there will be pooled urine collection for urine PK analysis also in these patients (Table 9).

The concentration of fitusiran will be determined using a validated assay. Full details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

## 7.5. Safety Assessments

The assessment of safety during the course of the study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, physical examinations, ECG findings, and laboratory tests.

Safety data will be periodically reviewed over the course of the study by the DMC as described in Section 4.6.

### 7.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1), and will include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured predose in the seated or supine position, after the patient has rested comfortably for 10 minutes.

Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

For the safety of the patient, additional vital sign assessments may be added at the discretion of the Investigator.

Vital signs results will be recorded in the eCRF.

### 7.5.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF.

### 7.5.3. Physical Examination

Full and directed physical examinations will be conducted as specified in the Schedule of Assessments (Table 1); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

Full physical examinations will include the examination of the following: general appearance, head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal and dermatological systems; thyroid, lymph nodes, and neurological status.

Directed physical examinations will include the examination of the following systems with attention to evaluation for signs and symptoms of thrombosis, bleeding, and arthropathy: neurologic, chest/respiratory, heart/cardiovascular, dermatological/skin, gastrointestinal/liver, and musculoskeletal/extremities. Other organ systems may be evaluated as indicated by patient symptoms. In patients undergoing a surgical procedure, a directed physical examination will also be performed as specified in the Perioperative Schedule of Assessments (Table 10).

Physical examination notes regarding any observed abnormalities will be recorded on the eCRF.

### 7.5.4. Electrocardiogram

Triplicate standard 12-lead ECGs, with readings approximately 1 minute apart, will be recorded as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 5 minutes before each ECG is obtained. The electrophysiological parameters assessed will be rhythm, ventricular rate, RR interval, PR interval, QRS duration, QT interval, Bazett-corrected QT interval (QTcB), and Fridericia corrected QT interval (QTcF).

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator. Recordings will be archived according to the Study Manual.

### 7.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after IMP administration, the test should be repeated and followed up at the discretion of the Investigator until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 5 and will be assessed as specified in the Schedule of Assessments (Table 1).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 5 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions.

Clinical laboratory assessments may be collected at the clinical site or at home by a trained healthcare professional. It is preferred that clinical laboratory assessments be drawn via peripheral draw (ie, fresh stick), however in cases where peripheral access is not possible existing indwelling venous access may be utilized.

Please see Section 6.2.3.1 for the LFT monitoring and dosing plan.

**Table 5: Clinical Laboratory Assessments**

| | |
|---|---|
| **Hematology** | |
| Hematocrit | Neutrophils, absolute and % |
| Hemoglobin | Lymphocytes, absolute and % |
| RBC count | Monocytes, absolute and % |
| WBC count | Eosinophils, absolute and % |
| Mean corpuscular volume | Basophils, absolute and % |
| Mean corpuscular hemoglobin | Platelet count |
| Mean corpuscular hemoglobin concentration | CD4 in HIV-positive patients (at Screening only) |
| **Serum Chemistry** | |
| Sodium | Potassium |
| BUN | Phosphate |
| Creatinine and eGFR (using the MDRD formula) | Albumin |
| Glucose | Calcium |
| Chloride | Carbon dioxide |
| **Liver Function Tests (LFTs)** | |
| AST | ALP |
| ALT | Bilirubin (total and direct) |
| GGT | |
| **Coagulation** | |
| Prothrombin time | Activated partial thromboplastin time |
| INR | Fibrinogen |
| D-dimer[a] | Prothrombin fragment 1, 2 |
| **Factor Activity** | |
| FVIII activity for patients with hemophilia A | FIX activity for patients with hemophilia B |
| **Urinalysis** | |
| Visual inspection for appearance and color | Bilirubin |
| pH (dipstick) | Nitrite |
| Specific gravity | RBCs |
| Ketones | Urobilinogen |
| Glucose | Leukocytes |
| Protein | Microscopy (if clinically indicated) |

**Table 6: Hepatic Assessments in Patients who Experience LFT Elevations**

| | |
|---|---|
| **Extended Hepatic Panel** | |
| Herpes Simplex Virus 1 and 2 antibody IgM, IgG | Herpes Zoster Virus IgM, IgG |
| HIV 1 and 2a | HHV-6 |
| Cytomegalovirus antibodies, IgM, IgG | HBs Ag, HBc antibody IgM and IgG |
| Anti-nuclear antibodies | Epstein-Barr Virus antibodies, IgM and IgG |
| Anti-smooth muscle antibodies | Anti-mitochondrial antibodies |
| HCV antibody | HAV antibody IgM |
| HCV RNA PCR – qualitative and quantitative | HEV antibody IgM |
| **Imaging** | |
| Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant | |
| **Focused Medical and Travel History** | |
| Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies | Alcohol consumption |
| Other potentially hepatotoxic agents including any work-related exposures | Recent travels to areas where hepatitis A or E is endemic |

Note: All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBs Ag=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; PT=prothrombin time; RNA=ribonucleic acid

[a] HIV testing will not be performed where prohibited by local regulations.

#### 7.5.5.2. Immunogenicity

Blood samples will be collected to evaluate antidrug antibodies (ADAs) to fitusiran. Blood samples for ADA testing must be collected within 4 hours before IMP administration as specified in the Schedule of Assessments (Table 1). In addition, a blood sample to evaluate ADAs will be collected at the ET visit, if applicable.

Details regarding the processing, shipping, and analysis of the samples are provided in the Laboratory Manual.

### 7.5.6. Adverse Events

#### 7.5.6.1. Definitions

**Adverse Event**

According to the International Conference on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical

investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Since bleeding episodes are recorded as an efficacy assessment of fitusiran, these will not be treated as AEs unless they meet any of the SAE criteria listed in Section 7.5.6.1.

**Serious Adverse Event**

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).
- Bleeding episodes will be recorded for efficacy assessment of fitusiran and will not be treated as AEs unless they meet any of the above criteria for SAEs.

**Adverse Events of Special Interest**

The following events are considered to be AEs of special interest (AESI):

- ALT or AST elevations >3× ULN
- Suspected or confirmed thrombosis
- Severe or serious ISRs, ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections) or, those that lead to temporary dose interruption or permanent discontinuation of fitusiran
- Systemic injection associated reactions (IARs), defined as hypersensitivity reactions which are related or possibly related to IMP.

#### 7.5.6.3. Serious Adverse Events and Adverse Events of Special Interest Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 7.5.6.1 and any AESI must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to IMP.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to IMP, and
- Investigator/site information

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to IMP, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

#### 7.5.6.4. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

#### 7.5.6.5. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

#### 7.5.6.6. Pregnancy Reporting

There will only be male patients in this study.

The reporting of any pregnancy outcome for a female partner of a male patient participating in this study that results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly should be reported to the Investigator, who will then report this to

the Sponsor or designee. The pregnancy outcome is to be recorded on the pregnancy reporting form.

#### 7.5.6.7. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. Overdose must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

#### 7.5.6.8. Guidelines for Reporting Product Complaints/Medical Device Incidents (Including Malfunctions)

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels, or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

## 7.6. Other Assessments

### 7.6.1. Patient-reported Outcomes

Patient-reported outcomes will be utilized in this study where available to assess HRQOL, physical activity, and treatment satisfaction and health utility. The age of the patient at randomization will determine which age-specific questionnaires will be utilized, and will be in force for the study duration. All completed questionnaires or instrument forms for the patient-reported outcome assessments described below will be collected, entered into a database, and archived according to the Study Manual.

The Sponsor or designee will provide the translations for all survey instruments, where translations are available. The sites must not translate any survey instruments.

#### 7.6.1.1. HRQOL Instruments: Haem-A-QOL and Haemo-QOL

The Hemophilia Quality of Life Questionnaire for adults (Haem-A-QOL) and Hemophilia Quality of Life Questionnaire for children and adolescents (Haemo-QOL) are psychometrically tested QOL assessment instruments for patients with hemophilia. [13] The Haem-A-QOL will be provided to patients ≥17 years of age, and includes 46 items contributing to 10 QOL domains (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality). Scoring for each item is based on a 5-point Likert scale (never, rarely, sometimes, often, and all the time), and higher scores represent greater impairment.

The Haemo-QOL (Children's short version for age groups II/III [8-16 years of age]) will be provided to patients <17 years of age, to self-complete as specified in the Schedule of

Assessments (Table 1). The same questionnaire used during the Baseline visit will be utilized throughout the study.

#### 7.6.1.2. TSQM-9

The Treatment Satisfaction Questionnaire for Medication (TSQM) will assess patient satisfaction with treatment. The TSQM is a validated psychometric tool that provides a general measure of patient satisfaction with medication.[14] Where available, the TSQM questionnaire will be distributed to patients to self-complete as specified in the Schedule of Assessments (Table 1).

#### 7.6.1.3. HAL

The Hemophilia Activities List (HAL) and pediatric HAL (pedHAL) questionnaires will assess subjective functional ability to perform activities of daily living.[15] The HAL will be assessed in patients ≥18 years of age, and the pedHAL will be assessed in patients <18 years of age. Where available, the HAL questionnaire will be distributed to patients to self-complete as specified in the Schedule of Assessments (Table 1).

#### 7.6.1.4. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of QOL outcome.[16] It consists of a questionnaire pertaining to 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and a visual analog scale). Scoring of the questionnaire is based on 5 degrees of disability (none, slight, moderate, severe, or extreme). Scoring of the visual analog scale is based on a visual scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Higher scores indicate better health status. The questionnaires will be completed by patients as specified in the Schedule of Assessments (Table 1).

### 7.6.2. Weight-adjusted Consumption of Bypassing Agents

Bypassing agent dose will be recorded by the patient in the eDiary and reviewed by the Investigator (and Sponsor or delegate) for the study duration to assess on-demand BPA usage, as treatment of breakthrough bleeding episodes. Weight-adjustment will be calculated programmatically.

### 7.6.3. HJHS

The HJHS is a tool for assessment of joint health in subjects with hemophilia.[17] Joint health status will be assessed via the HJHS, as administered by a healthcare professional trained in the use of anthropometric measures, as specified in the Schedule of Assessments (Table 1). Completed HJHS score forms will be collected and archived according to the Study Manual.

## 8. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

Patients who discontinue treatment during the study will be encouraged to continue recording bleeding episode data.

Sensitivity analyses will be performed to evaluate the impact of missing data under different missing data mechanisms and details will be specified in the statistical analysis plan.

#### 8.2.5.2. Secondary Endpoints

The bleeding episodes in the treatment period (Day 1 to Day 246), spontaneous bleeding episodes in the efficacy period, joint bleeding episodes in the efficacy period, and bleeding episodes in the onset period will be analyzed using the same method as primary analysis of ABR. Summary statistics, including the median and interquartile range for annualized rates of these endpoints will be reported.

The change from baseline in physical health score and total score of Haem-A-QOL will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects of treatment arm, baseline Haem-A-QOL physical health score and total score, and the number of bleeding episodes in the 6 months prior to study entry (≤10 vs >10) as covariates. Domain scores for Haem-A-QOL and their changes from baseline will be summarized descriptively by scheduled visit.

#### 8.2.5.3. Exploratory Endpoints

Details of the analyses for the exploratory endpoints will be described in the SAP.

### 8.2.6. Pharmacodynamic Analysis

AT and thrombin levels will be summarized descriptively by scheduled visit. Mixed models repeated measures analyses may be performed as deemed appropriate. Correlation between AT and thrombin levels may be explored.

### 8.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using a population PK approach on patients in the fitusiran arm. The details of the analysis will be presented in a separate population PK analysis plan.

In addition to performing population PK analyses, the following PK parameters will be included in an analysis of East Asian patients in the fitusiran arm at East Asian sites: maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($t_{max}$), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), apparent clearance (CL/F), and apparent volume of distribution (V/F); these parameters will be estimated during the fitusiran treatment period using non-compartmental analysis. Other parameters may be calculated, if deemed necessary.

### 8.2.8. Safety Analyses

Extent of exposure will be summarized. Safety will be based on all AEs having onset (start or worsening in severity) within the study and on the Safety Analysis Set. Incidence of AEs, AEs by maximum severity, AEs by relationship to study medication, SAEs and AEs leading to discontinuation of treatment will be presented.

Descriptive statistics will be provided for clinical laboratory data, ECG and vital signs. Laboratory shift tables from baseline to worst post-baseline values may be presented.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

Adverse events will be classified according to the MedDRA System Organ Class and Preferred Term. Prior and concomitant medications will be classified according to the World Health Organization (WHO) drug dictionary.

### 8.2.9. Other Analysis

Antidrug antibody results will be summarized descriptively.

### 8.2.10. Interim Analysis

No interim analysis is planned.

# 9. STUDY ADMINISTRATION

## 9.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

### 9.1.1. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative (defined as an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial) and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient’s legally authorized representative.

## Table 10: Perioperative Schedule of Assessments in Patients Undergoing Operative Procedures

| | Perioperative Evaluation Period[a] | | | | |
|---|---|---|---|---|---|
| | **Preoperative Screening** | **Dental/Surgical Procedure Visit** | **Postoperative Visit 1** | **Postoperative Visit 2** | **Postoperative Visit 3** |
| | **SDay -3 to SDay -1** | **SDay 0** | **SDay 1[b]** | **SDay 2 to 14[c]** | **SDay 28[d]** |
| Directed Physical Examination[d] | X | | | | X |
| Vital Sign Measurements[e] | X | | | | X |
| Clinical Laboratory Assessments[f] | X | X[h] | X | X | X |
| TG | X | X[g,h] | X[k] | X[k] | X[k] |
| AT Activity Level | X | X[i] | | | |
| FVIII/IX Levels[g] | X | X[g,h] | X[k] | X[k] | X[k] |
| Perioperative Questionnaire | | X[j] | X | X | |
| Completion of Hemostatic Treatment Coverage | | | | X[l] | X[l] |

Note: Any operative procedure dates (SDay -3 to SDay 28) may overlap with the study Schedule of Assessments (Table 1)
Abbreviations: APTT=activated partial thromboplastin time; AT=antithrombin; BPA=bypassing agent; SDay=surgery day; TG=thrombin generation

[a] During Perioperative Evaluation Period, AEs and concomitant medications will be collected continuously per study Schedule of Assessments (Table 1).

[b] Assessments to be completed within 24 hours (±12 hours) from the time of end of the procedure.

[C] Visit may occur anytime between SDay 2 to SDay 14, postoperatively, on a day to be determined by the Investigator. If multiple visits are planned between Days 2-14 after the procedure, the perioperative questionnaire for Postoperative Visit 2 should be completed on the day of the last visit.

[d] Directed physical examination (see Section 7.5.3)

[e] Vital signs will be the same as conducted in the clinical study protocol Schedule of Assessments (Table 1).

[f] Clinical laboratory assessments will include coagulation, hematology and biochemistry (Table 5).

[g] If factor or BPA administration and the surgical procedure occur at the study center visit, one sample should be collected pre-factor/BPA administration and two samples should be collected post- factor/BPA administration on the day the procedure. The pre- factor/BPA sample may be collected any time before factor or BPA administration. The post- factor/BPA samples should optimally be collected at 10 min (±5 min) and 60 min (±10 min) after factor or BPA administration. The actual times of collections should be recorded.

[h] If the operative procedure is not performed at a study center, the assessment is recommended.

[i] Not necessary if captured at preoperative screening.

[j] Hemostatic efficacy is to be assessed intraoperatively with the perioperative questionnaire on the day of the procedure (SDay 0); assessment may be completed up to 8 hours postoperatively. The perioperative questionnaire will also be completed at Postoperative Visit 1 and Visit 2. It is recommended that the Investigator complete this assessment in consultation with the surgeon or dentist who performed the operative procedure.

[k] If factor or BPA administration occurs at the study center visit, then assessments should be collected at the following time points: pre- factor/BPA administration; 10 min (±5 min) post-factor/BPA administration; and 60 minutes (±10 min) post-factor/BPA administration. The actual times of collection should be recorded.

[l] The date/time of when perioperative hemostatic treatment and thromboprophylaxis (if applicable) coverage was completed will be captured. If completed at Postoperative Visit 2, the date/time of completion should be recorded and the SDay 28 visit is not required.

## 11.6. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

### 11.6.1. Amended Protocol 01

Primary changes:

- Updated clinical development status text to account for a patient death, which was reported in a patient with cerebral venous sinus thrombosis (CVST) in the ALN-AT3SC-002 study (Phase 1/2 open-label extension study)
- Additional safety measures were implemented to mitigate risk of thrombosis in the lowered-AT setting, including: revised bleed management guidelines to allow standard BPA regimens only up to the first 7 days following fitusiran dosing; added recommendations for monitoring and management of thrombotic events; added clarification of definitions for bleeding episodes; revised recommendations for management of sepsis, and adding additional exploratory laboratory assessments
- Frequency of directed physical exams to monthly
- Updated Benefit-Risk Assessment section accordingly with respect to the above new safety monitoring
- Added Patient Education Module training to Schedule of Assessments
- Clarification added that Adverse Events should include review for signs and symptoms of thrombosis at each visit
- Clarifications added to the Perioperative Schedule of Assessments
- Addition of acetaminophen restriction to <4 grams per day
- Stipulation added that antifibrinolytics may be used as single agents, but may not be used in combination with factor or BPA
- Addition that aPCC and rFVIIa are not recommended for use as combination therapy
- Revised bleed management recommendations following discontinuation of fitusiran; standard on-demand dosing with BPAs is permitted when AT residual activity level returns to ~60% (per the central laboratory)
- Addition of prothrombin activation fragment 1,2 to the coagulation panel, as exploratory marker of hemostasis
- Addition of new stipulation for patients who present to the study site for management of bleed symptoms, samples will be collected pre-treatment and post-treatment with factor or BPA for the exploratory purposes of characterizing thrombin generation and other coagulation parameters
- Other minor corrections applied.

**Study Design**

The ATLAS-INH trial (ALN-AT3SC-003 [Sanofi Genzyme EFC14768]) is a multicenter, multinational, randomized, open-label Phase 3 study designed to evaluate the efficacy and safety of fitusiran in male patients aged ≥12 years, with hemophilia A or B and inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX), who are not receiving prophylactic therapy.

Eligible patients will be randomized in a 2:1 ratio to:

- **Fitusiran treatment arm**: Fitusiran 80 mg administered subcutaneously (SC) as prophylaxis once monthly, with use of on-demand BPAs for treatment of breakthrough bleeding episodes
- **On-demand arm**: On-demand BPAs for treatment of breakthrough bleeding episodes

On-demand use of BPAs is defined as the use of these agents as needed for episodic bleeding and not on a regular regimen intended to prevent spontaneous bleeding. Throughout the study, patients in the fitusiran treatment arm may receive on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate.

Bleeding events and doses of BPAs administered during the conduct of the study will be recorded in an electronic Diary (eDiary). Safety, quality of life, and pharmacodynamic, and pharmacokinetic data will also be collected.

All patients will be treated for a total of 9 months; patients randomized to the fitusiran treatment arm will receive a total of 9 SC injections of fitusiran. Because the full PD effect of fitusiran is not achieved until approximately 28 days after receiving the first dose, efficacy will be assessed during the final 8 months on study (Day 29 to Month 9).

An independent data monitoring committee (DMC) will oversee the safety and overall conduct of this study. The DMC will perform periodic reviews of data during the course of the clinical trial, and on an ad hoc basis for review of emergent safety data, as defined in the DMC Charter for this clinical trial.

Patients from both the fitusiran and on-demand treatment arms who complete the study may be eligible for participation in an open-label extension study. Following final fitusiran dose, for patients in the fitusiran treatment arm patients who do not enroll in the extension study, AT activity level will be monitored at monthly intervals until returning to an activity level of approximately 60% (per the central laboratory) or per Investigator discretion in consultation with the study Medical Monitor.

**Number of Planned Patients**

Approximately 54 patients will be randomized, including approximately 5 patients with hemophilia B and approximately 5 adolescents (≥12 to <18 years of age).

**Diagnosis and Main Eligibility Criteria**

This study will include males with severe hemophilia A or B with inhibitors, aged ≥12 years, who have had a minimum of 6 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening. Diagnosis of severe hemophilia A or B will be based on a central laboratory measurement or documented medical record evidence of FVIII level <1% or FIX level ≤2% at Screening.

Patients with inhibitors must have used bypass agents on demand to manage bleeding episodes for at least the last 6 months prior to Screening and must meet one of the following Nijmegen-modified Bethesda assay results criteria: 1) Inhibitor titer of ≥0.6 BU/mL at Screening, OR 2) Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of 2 consecutive titers ≥0.6 BU/mL, OR 3) Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of anamnestic response.

| Abbreviation or Specialist Term | Explanation |
|---|---|
| MAD | Multiple ascending dose |
| MDRD | Modification of Diet in Renal Disease |
| MMRM | Mixed effect repeated measures |
| mRNA | Messenger ribonucleic acid |
| NHP | Non-human primates |
| NOAEL | No observed adverse effect level |
| PD | Pharmacodynamics |
| PedHAL | Pediatric HAL |
| PK | Pharmacokinetics |
| PP | Per-protocol |
| PT | Prothrombin time |
| QOL | Quality of Life |
| RNAi | Ribonucleic acid interference |
| rVIIa | Recombinant factor VIIa |
| SAD | Single ascending dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard deviation |
| SDay | Surgery day |
| siRNA | Small interfering ribonucleic acid |
| SSC | Scientific Standardization Committee |
| SUSAR | Suspected unexpected serious adverse reactions |
| $t_{1/2\beta}$ | Elimination half-life |
| $t_{max}$ | Time to maximum plasma concentration |
| TG | Thrombin generation |
| TSQM | Treatment Satisfaction Questionnaire for Medication |
| ULN | Upper limit of normal |
| V/F | Apparent volume of distribution |

maximal achievable reduction in ABR, in which the majority of patients may achieve >75% AT lowering, the therapeutic target. Weight was not a significant covariate in the model, suggesting no advantage to weight-based dosing.

The safety of fitusiran has been evaluated in healthy volunteers and patients with moderate to severe hemophilia A and in patients with moderate to severe hemophilia B in the ongoing Phase 1 and Phase 1/2 studies and overall, supports monthly administration of the 80 mg dose in this study. Full details of the safety findings from the Phase 1 and Phase 1/2 studies are presented in the Investigator's Brochure.

## 1.5. Benefit-Risk Assessment

Based on the available clinical data (see Section 1.2.2), fitusiran, administered subcutaneously as a once-monthly fixed-dose regimen, may be able to offer potentially reduced bleeding rates for patients receiving factor concentrate or BPA treatment prophylactically or on-demand. Further, the pharmacodynamic profile of fitusiran results in consistent reduction of AT and therefore may provide more consistent increase in thrombin generation and hemostatic protection throughout the dosing interval. The clinical experience to date suggests that in hemophilia A or B patients, with or without inhibitors, fitusiran treatment is associated with reductions in AT, increases in thrombin generation, and reduction of the number of bleeding episodes.

Given the mechanism of action of fitusiran, mode of administration, and available safety data, the possible risks associated with the use of fitusiran include thrombosis, liver transaminase abnormalities, and injection site reactions (ISRs). Due to the underlying pro-hemostatic effect of fitusiran, the concomitant treatment of breakthrough bleeding episodes with factor or BPA particularly at doses higher than recommended in the protocol may confer an increased risk of thrombosis. For summary of the completed Phase 1 study, and preliminary interim data from the Phase 1/2 extension study of fitusiran, see Section 1.2.2; further details of fitusiran studies are presented in the Investigator's Brochure.

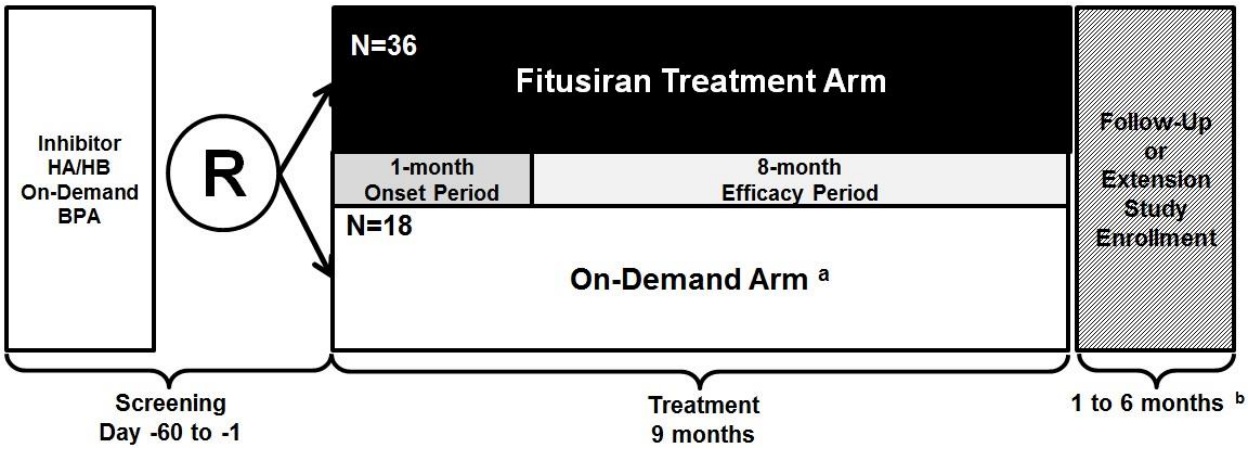
This clinical protocol has exclusion criteria intended to minimize the risk of thrombosis, liver transaminase abnormalities, and serious ISRs. With respect to the risk of thrombosis, the protocol includes detailed guidance and oversight on treatment of breakthrough bleeding episodes with reduced factor/BPA dosing (Section 6.3.1), and management of operative procedures that occur while patients are on fitusiran (Section 6.6). The protocol also excludes patients with evidence of liver disease (including active viral hepatitis) and stipulates ongoing monitoring for elevated transaminases (Section 6.2.3.1). The safety of trial patients will be overseen by an independent DMC (Section 4.7).

# 2. OBJECTIVES

## 2.1. Primary Objective

- To evaluate the efficacy of fitusiran compared to on-demand treatment with BPAs, as determined by the frequency of bleeding episodes.

**Figure 1: Study Design**




Abbreviations: BPA = bypassing agent; HA/HB = hemophilia type A / hemophilia type B; R = randomized
[a] On-demand local BPA as routinely prescribed by physician per local standard practice.
[b] Fitusiran treatment arm patients who do not enroll in the extension study: AT activity level will be monitored at monthly intervals following the final fitusiran dose until activity levels return to approximately 60% (per the central laboratory) or per Investigator discretion in consultation with the study Medical Monitor.

## 4.2. Duration of Treatment

The duration of treatment with fitusiran is 9 months. The estimated total time on study, inclusive of screening, for each patient is up to 11 months for all patients who enroll in the extension study and patients in the on-demand arm who do not enroll in the extension study. The estimated total time on study may be up to 17 months in fitusiran treatment arm patients who do not enroll in the extension study due to the requirement for an additional 6 months of follow-up for monitoring of AT levels.

## 4.3. Number of Patients

Approximately 54 patients will be randomized, including approximately 5 patients with hemophilia B and approximately 5 adolescents (≥12 to <18 years of age).

## 4.4. Method of Assigning Patients to Treatment Groups

Patients will be randomized 2:1 to the fitusiran treatment arm and the on-demand arm. Randomization will be stratified by the number of bleeding episodes in the 6 months prior to Screening (≤10 vs >10).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the interactive response system (IRS). The Investigator or his/her delegate will contact the IRS after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. A combination of the site number and patient identification number will create the unique patient identifier.

bleeding.[10, 11] If a clinical determination is made that AT correction is desirable for a fitusiran-treated patient in the setting of sepsis, this may be initiated per Investigator discretion.

## 6.8. Contraceptive Requirements

All study patients will be male, and there are no contraceptive requirements for this study except where required by local regulations.

Details of fitusiran toxicology studies are presented in the Investigator's Brochure.

## 6.9. Treatment Compliance

Compliance with scheduled clinic visits (Table 1), and patient use of eDiary to record data as required, will be monitored by study staff over the 9-month treatment duration.

## 6.10. Alcohol Restrictions

Patients will be required to limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits (approximately 1 fluid ounce) = ½ pint of beer [approximately 284 mL]) per day (no more than 14 units per week) for the duration of the study.

# 7. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1. Additional information on the collection of study assessments will be detailed in the Study Manual.

## 7.1. Screening/Baseline Assessments

An informed consent form (ICF) or assent form that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening/Baseline procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF and/or assent form.

Patient demographic and medical history will be obtained at Screening. Medical history must include documentation of BPA prescriptions (in the medical or pharmacy record) and documentation of reported number of bleeding episodes over the last 6 months. Patients will be screened to ensure that they meet all of the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the medical monitor.

To complement medical records, information regarding health resource use will be collected as specified in the Schedule of Assessments (Table 1), including days missed from work/school (as appropriate) and days not able to perform normal activities outside of work/school due to hemophilia, physician office visits, hemophilia treatment site visits, emergency room visits (reason and number), hospitalizations (reason, dates of hospitalization and associated length of stay).

**Table 5: Clinical Laboratory Assessments**

| | |
|---|---|
| **Thrombophilia Screening** | |
| Protein C deficiency | Protein S deficiency |
| Factor V Leiden (genetic testing) | Prothrombin mutation (genetic testing) |
| **Hepatic Tests** | |
| Hepatitis A, including:<br>HAV antibody IgM and IgG | Hepatitis C, including:<br>HCV antibody<br>HCV RNA PCR – qualitative and quantitative assays |
| Hepatitis B, including:<br>HBs Ag, anti-HBc antibody, IgM and IgG | Hepatitis E, including:<br>HEV antibody IgM and IgG |
| **Immunogenicity** | |
| Antidrug Antibodies | |

Note: All assessments will be measured in central laboratory.

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CD4=cluster of differentiation 4; eGFR=estimated glomerular filtration rate; FIX=factor IX; FVIII=factor VIII; GGT= gamma glutamyl transferase; HAV=hepatitis A virus; HBs Ag=hepatitis B virus surface antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; INR=International normalized ratio; MDRD=Modification of Diet in Renal Disease; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid; WBC=white blood cell.

[a] Will not be communicated to investigational sites.

#### 7.5.5.1. Additional Laboratory Assessments

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the study Medical Monitor; results may be collected and should be included in the clinical database.

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 6.2.3.1. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 5, AT levels, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring and dose modification will also be performed as outlined in Section 6.2.3.1.

### Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

| | |
|---|---|
| Mild: | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Moderate: | Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money) |
| Severe: | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an AE |

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

### Relationship of the Adverse Event to Study Treatment

The relationship of each AE to study treatment should be evaluated by the Investigator using the following criteria:

| | |
|---|---|
| Definitely related: | A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. |
| Possibly related: | A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear. |
| Unlikely related: | A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals, or underlying disease provide plausible explanations. |
| Not related: | A clinical event, including laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology. |

The primary efficacy and safety analyses will be performed after all patients have either finished the 9-month treatment period or discontinued from the study.

## 8.1. Determination of Sample Size

Assuming a mean ABR of 18 with standard deviation (SD) = 14 in the on-demand arm (patients randomized to receive on-demand BPAs) and a mean ABR of no more than 4 with SD = 6 in the fitusiran treatment arm (patients randomized to receive fitusiran) in either the efficacy period or treatment period, with a sample size of 14 evaluable patients in on-demand arm and approximately 28 evaluable patients in the fitusiran treatment arm, it is projected that the study will have greater than 90% power for testing treatment difference in mean ABRs. This power estimation was based on negative binomial regression model with a 2-sided type I error rate of 0.05.

The planned sample size is 54 randomized patients assuming a 20% drop-out rate.

## 8.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report.

### 8.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- Intent-to-treat (ITT) Analysis Set: All randomized patients. All by-treatment analyses based on the ITT analysis set will be according to the randomized treatment arm.
- Safety Analysis Set: All patients who received at least 1 dose of fitusiran or were randomized to on-demand arm. All by-treatment analyses based on the safety analysis set will be according to the actual treatment received.
- Per-protocol Analysis Set: All patients in the ITT set who had no major protocol deviations. Major deviations will be specified in the SAP.
- PK Analysis Set: All patients who receive at least 1 dose of fitusiran and have at least one postdose blood sample for PK parameters and who have evaluable PK data.
- Operative Procedure Analysis Set: All patients who received at least 1 dose of fitusiran and underwent at least 1 operative procedure during the study.

### 8.2.2. Examination of Subgroups

Exploratory subgroup analysis on ABR will be conducted for the primary endpoint and selected secondary endpoints. Description of the subgroups will be detailed in the SAP.

### 8.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

### 9.1.2. Ethical Review

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

### 9.1.3. Study Documentation, Confidentiality, and Records Retention

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.

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 IRB/IEC members, and by inspectors from regulatory authorities.

### 9.1.4. End of the Study

The end of the study is defined as last patient last visit.

### 9.1.5. Discontinuation of the Clinical Study

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

## 11.3. International Society on Thrombosis and Hemostasis Guideline for Assessment of Treatment Response

ISTH recommendations [12] are provided in the table below for assessment of treatment response (Table 11).

**Table 11: Assessment of Treatment of Acute Joint/Muscle Bleeding Episodes**

| Category | Response |
|---|---|
| Excellent | Complete pain relief within 8 hours and/or complete resolution of signs of bleeding after the initial injection and not requiring any further replacement therapy for relief of persistent symptoms and signs in the same joint within 72 hours |
| Good | Significant pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but requiring more than one dose of replacement therapy within 72 hours for complete resolution |
| Moderate | Modest pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection and requiring more than one injection within 72 hours but without complete resolution |
| None | No or minimal improvement, or condition worsens, within approximately 8 hours after the initial injection |

## 11.4. Bleed Severity Definitions

The definitions of bleed severity are shown in Table 12.

**Table 12: Bleed Severity Definitions**

| Bleed Severity | Definition |
|---|---|
| Minor | Early joint bleeding; mild muscle bleeding; or mild bleeding (any other location) |
| Moderate | Definite joint bleeding; moderate muscle bleeding; moderate bleeding (any other location); known trauma (other than head trauma or fractures) |
| Major | Severe bleeding that is life- or limb-threatening; including fractures and head trauma |

## 11.5. Country-Specific Requirements

Country-specific requirements are provided in separate country-specific protocol.