SANOFI GENZYME

NCT03549871

# CLINICAL STUDY PROTOCOL

## ALN-AT3SC-009 (Sanofi Genzyme EFC15110)

| | |
|---|---|
| **Protocol Title:** | ATLAS-PPX: an open-label, multinational, switching study to describe the efficacy and safety of fitusiran prophylaxis in patients with hemophilia A and B previously receiving factor or bypassing agent prophylaxis. |
| **Investigational Drug:** | Fitusiran (SAR439774 [formerly Alnylam ALN-AT3SC]) |
| **EudraCT Number:** | 2016-004087-19 |
| **WHO Number:** | U1111-1217-3270 |
| **IND Number:** | 125632 |
| **Protocol Date:** | Original protocol, 23 May 2017<br>Amended protocol 01, 28 November 2017<br>Amended protocol 02, 31 May 2018<br>Amended protocol 03, 24 August 2018<br>Amended protocol 04, 18 December 2018<br>Amended protocol 05, 25 November 2020<br>Amended protocol 06, 08 December 2020 |
| **Sponsor:** | Genzyme Corporation,<br>50 Binney Street,<br>Cambridge, MA 02142, USA |
| **Sponsor Contact:** | [redacted] |

**PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE**

# DOCUMENT HISTORY

| Document | Country-specificity if applicable | Date, version |
|---|---|---|
| Amended protocol 06 | NA | 08 December 2020, version 1 (electronic 4.0) |
| Amended protocol 05 | NA | 25 November 2020, version 1 (electronic 3.0) |
| Amended protocol 04 | United States, Japan | 18 December 2018, version 1 (electronic 2.0) |
| Amended protocol 03 | Republic of Ireland | 24 August 2018, version 1 (electronic 2.0) |
| Amended protocol 02 | NA | 31 May 2018, version 1 (electronic 1.0) |
| Amended protocol 01 | NA | 28 November 2017, version 1 (electronic 1.0) |
| Original protocol | NA | 23 May 2017, version 1 (electronic 1.0) |

## Amended protocol 06 (08 December 2020)

This amended protocol (amendment 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

# OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to minimize the time between 2 antithrombin (AT) measurements if the first AT result is <15%.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table1: Schedule of assessments | Sentence added to footnotes "n": For the AT assessments, upon the first AT activity level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the results. | To mandate a second AT activity level within 1 week of site receipt of an initial AT level result <15%. |
| Section 6.2.3.2: Antithrombin level criteria for a dose adjustment | Text changed from "Patients receiving fitusiran at a dose of 50 mg Q2M with more than 1 AT activity measurement <15% at any time during the study must permanently discontinue fitusiran." to "Upon the first AT level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the results. If this result is <15%, this will be considered the second AT activity level <15%. Patients receiving fitusiran at a dose of 50 mg Q2M with more than 1 AT activity level <15% at any time during the study must permanently discontinue fitusiran ." | To specify and address dose adjustment based on AT activity levels. |
| Section 11.7.5 Amended Protocol 05 | New section added. | To document protocol amendments history. |
| Throughout | Minor editorial, typo error corrections and document formatting revisions. | Minor, therefore, have not been summarized. |

# NAMES AND ADRESSES OF:

**MONITORING TEAM'S REPRESENTATIVE**

| | |
|---|---|
| Name: | |
| Address: | |
| Tel: | |
| Fax: | |
| E-mail | |

**SPONSOR**

| | |
|---|---|
| Name: | Genzyme Corporation |
| Address: | 50 Binney Street<br>Cambridge, MA 02142, USA |

# PROTOCOL SYNOPSIS

**Protocol title**

ATLAS-PPX: an open-label, multinational, switching study to describe the efficacy and safety of fitusiran prophylaxis in patients with hemophilia A and B previously receiving factor or bypassing agent prophylaxis.

**Product name**

Fitusiran (INN); SAR439774 (formerly Alnylam ALN-AT3SC)

**Indication**

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent (≥12 years old) hemophilia A or B patients

**Phase**

3

**Study center(s)**

The study will be conducted at approximately 70 clinical study centers worldwide.

**Objectives**

**Primary**

- To characterize the frequency of bleeding episodes while receiving fitusiran treatment, relative to the frequency of bleeding episodes while receiving factor or bypassing agent (BPA) prophylaxis

**Secondary**

- To characterize the following while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis:
  - 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 characterize the frequency of bleeding episodes during the onset and treatment periods in patients receiving fitusiran
- To characterize the safety and tolerability of fitusiran
- To characterize the annualized weight-adjusted consumption of factor/BPA while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis

**Exploratory**

- To characterize the effects of fitusiran on the following patient-reported outcomes while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis:
  - Patient satisfaction with fitusiran
  - Patient activity
  - HRQOL in adolescents (≥12 to <17 years of age)
- To characterize the pharmacodynamic (PD) effect, pharmacokinetics (PK), and immunogenicity of fitusiran
- To characterize the effects of fitusiran on joint status while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis
- To characterize the effects of fitusiran on patient resource use, relative to receiving factor or BPA prophylaxis

**Endpoints**

**Primary**

- Annualized Bleeding Rate (ABR) in the fitusiran efficacy period and the factor or BPA prophylaxis period

**Secondary**

- Annualized spontaneous bleeding rate in the fitusiran efficacy period and the factor or BPA prophylaxis period
- Annualized joint bleeding rate in the fitusiran efficacy period and the factor or BPA prophylaxis period
- Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period
- ABR in the fitusiran onset period
- ABR in fitusiran treatment period
- Annualized weight-adjusted consumption of factor/BPA

**Exploratory**

- Change in the following in the fitusiran treatment period:
  - Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores
  - Haemophilia Activities List (HAL) score
  - Paediatric HAL (pedHAL) score
  - EuroQol-5 Dimensions (EQ-5D) score
  - 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 period
- Antithrombin (AT) activity level over time
- Thrombin generation over time
- Fitusiran plasma levels
- Change in patient resource use (eg, work/school attendance, visits to doctor/hospital)

**Safety**

- Incidence, severity, seriousness, and relatedness of adverse events

**Study design**

The ATLAS-PPX trial (ALN-AT3SC-009 [Sanofi Genzyme EFC15110]) is a multicenter, multinational, 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, who have switched from prior bypassing agent (BPA, Cohort A) or factor (Cohort B) prophylaxis. A subgroup of Cohort A patients will include hemophilia B patients with inhibitory antibodies to Factor IX who are not responding adequately to BPA prophylaxis treatment (historical ABR ≥20).

The study has 3 periods:

- 6-Month factor or BPA prophylaxis period in which patients will continue their prestudy, regularly scheduled prophylaxis regimen with factor concentrates or BPAs

  The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this 6-month BPA prophylaxis period and will start directly receiving fitusiran (in the 1-month onset period described below) after the screening period.
- 1-Month onset period in which patients receive their first dose of fitusiran while continuing their factor or BPA prophylaxis for up to 7 days
- 6-Month fitusiran efficacy period in which patients receive fitusiran as prophylaxis

Together, the 1-month onset period and the 6-month fitusiran efficacy period constitute the fitusiran treatment period.

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

Following the screening and prophylaxis periods or following the screening period for the subgroup of Cohort A enrolling directly into the fitusiran treatment period, all patients will be treated with fitusiran for a total of 7 months.

Throughout the study, patients may receive on-demand treatment for breakthrough bleeding episodes with factors or BPAs, as appropriate.

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 who complete the study may be eligible for participation in an open-label extension study. For 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.

For the United States specific requirements, see Section 11.6.1.1.

**Number of planned patients**

Approximately 80 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 50 patients without inhibitors (Cohort B). Approximately 18 patients with hemophilia B (including approximately 7 hemophilia B patients in Cohort A, among which are a subgroup of no more than 4 patients who are not responding adequately to BPA prophylaxis, and approximately 11 hemophilia B patients in Cohort B, and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment. For the United States specific requirements, see Section 11.6.1.1.

**Diagnosis and main eligibility criteria**

This study will include males with severe hemophilia A or B with or without inhibitors, aged ≥12 years, who have been prescribed prophylactic treatment with factor concentrates or BPAs for at least 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%.

Patients with inhibitors must have used BPAs for prophylaxis 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. The subgroup of patients in Cohort A patients must additionally meet the following criteria to be eligible to start treatment with fitusiran directly after the screening period: 1) Hemophilia B with inhibitory antibody to Factor IX as defined above; 2) Not responding adequately to BPA treatment (historical ABR ≥20) prior to enrollment; and 3) in the opinion of the Investigator, with approval of Sponsor Medical Monitor, 6-month BPA prophylaxis period should be omitted. A minimum of 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening is required.

Patients without inhibitors must have used factor concentrates for prophylaxis for at least the last 6 months prior to Screening and must meet each of the following criteria: 1) Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening, AND 2) No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening, AND 3) No history of immune tolerance induction therapy within the last 3 years prior to Screening. A minimum of 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening is required. For the United States specific requirements, see Section 11.6.1.1.

**Investigational product, dose and mode of administration**

Fitusiran is a subcutaneously (SC) administered GalNAc-conjugated siRNA targeting liver-expressed messenger RNA (mRNA) for AT.

Patients will receive open label fitusiran as an SC injection, for a total of 7 months; dosing will begin on Day 1 of the fitusiran treatment period.

**Reference therapy, dose and mode of administration**

During the factor or BPA prophylaxis period, patients will continue FVIII, FIX, or BPA prophylaxis as treatment for hemophilia on a regimen consistent with recommendations in the approved prescribing information, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding. Dose and mode of administration will be per Investigator discretion; bleeding episode management should be per the local standard practice for episodic use of factors or BPAs and as per Investigator discretion. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate into this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. All patients will continue to receive FVIII, FIX, or BPA prophylaxis for the first 7 days of the onset period. Subsequently, breakthrough bleeding episodes will be treated with on-demand factor or BPA therapy as necessary per the bleeding episode management guidelines. For the United States specific requirements, see Section 11.6.1.1.

**Duration of treatment**

The duration of treatment with fitusiran is 7 months. The estimated total time on study, inclusive of Screening, for each patient is up to 15 months for patients who enroll in the extension study except for patients in the subgroup of Cohort A, which is up to 9 months. The estimated total time on study may be up to 21 months (up to 15 months in patients in the subgroup of Cohort A) in 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.

**Statistical methods**

Sample size is based on clinical considerations. The efficacy analyses will be based on the efficacy analysis set, which includes all patients who received both factor or BPA prophylaxis and any dose of fitusiran in the study. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will be included in the safety analysis set but will not be part of the efficacy analysis set; however, their efficacy data will be presented separately. The primary endpoint and the secondary endpoints (spontaneous bleeding episodes and joint bleeding episodes) will be based on the bleeding events occurring in the factor or BPA prophylaxis period (Day -162 to Day -1) and the fitusiran efficacy period (Day 29 to Day 190). To avoid confounding treatment effect, bleed data following major surgery, antithrombin administration, major trauma, or the re-initiation of prophylaxis treatment with factors or BPAs after fitusiran discontinuation will be excluded from the primary analysis.

The number of bleeding episodes will be analyzed using a repeated measures negative binomial model with fixed effect of treatment period. The ratio of bleeding rates in the fitusiran efficacy period relative to the factor/BPA prophylaxis period and its 95% CI and p-value will be presented. The logarithm of bleeding episode follow-up time in each period for each patient will be used as an offset parameter in the model to account for any difference in follow-up duration. The p-value should be interpreted with caution. In addition, as a contrast Bayesian analyses will be performed to summarize the point estimates of the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty. In addition, estimated mean ABR and its 95% CI during each of the 2 periods and during the fitusiran onset period will be presented. The spontaneous bleeding episodes and the joint bleeding episodes will be analyzed using the same model as used in the primary analysis. Safety data will be summarized descriptively. The bleeding episodes in the fitusiran onset period and in the fitusiran treatment period will be analyzed using a negative binomial model with logarithm of follow-up time in the period as an offset parameter. Change in Haem-A-QOL physical health score and total score in the factor/BPA prophylaxis period and fitusiran treatment period will be summarized descriptively. A mixed model for repeated measures analysis may be performed as deemed appropriate. The annualized weight-adjusted consumption of factor/BPA injections will be summarized using descriptive statistics. For United States specific requirements see Section 11.6.1.1.

The above analyses will be done for Cohort A and Cohort B separately. A pooled analysis will be performed after all patients in the 2 cohorts have either finished the Month 7 visit during the fitusiran treatment period or discontinued from the study.

**Table 1 - Schedule of assessments**

| | | Factor or BPA prophylaxis period[a] | | | | | | Fitusiran treatment period[b] | | | | | | | | | | AT F/U[d,e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Onset period[b] | | Efficacy period | | | | | | | | |
| Study visit (Month) | Screening | Month -6 | Month -5 | Month -4 | Month -3 | Month -2 | Month -1 | Baseline | | Month 1 | | Month 2 | Month 3 | Month 4 | Month 5 | EOT Month 6 | EOS/ ET[c,d] Month 7 | Month 8 |
| Study day (±Visit Window) | -228 to -169 | Day -168 | Day -140 ±7 | Day -112 ±7 | Day -84 ±7 | Day -56 ±7 | Day -28 ±7 | Day 1 | Day 15 ±3 | Day 29 ±7 | Day 43 ±3 | Day 57 ±7 | Day 85 ±7 | Day 113 ±7 | Day 141 ±7 | Day 169 ±7 | Day 197 ±7 | Day 225 ±7 |
| Informed Consent/Assent | X | | | | | | | | | | | | | | | | | |
| Medical History[f] | X | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | | | |
| Enrollment | | X | | | | | | | | | | | | | | | | |
| eDiary Training[g] | X | | | | | | | | | | | | | | | | | |
| Physical Examination[h] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body Weight and Height[i] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-Lead ECG[j] | X | X | | | | | | X | | | | | | | | | X | |
| FibroScan OR FibroTest/APRI[k] | X | | | | | | | | | | | | | | | | | |
| TG Level[l] | X | | | | | | | X | X | X | X | X | X | X | X | X | X | X |

**Table 1 - Schedule of assessments**

| Study visit (Month) | Screening | Factor or BPA prophylaxis period[a] | | | | | | Fitusiran treatment period[b] | | | | | | | | | | AT F/U[d,e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Onset period[b] | | Efficacy period | | | | | | | EOT | EOS/ ET[c,d] | |
| | | Month -6 | Month -5 | Month -4 | Month -3 | Month -2 | Month -1 | Baseline | | Month 1 | | Month 2 | Month 3 | Month 4 | Month 5 | | Month 6 | Month 7 | Month 8 |
| **Study day (±Visit Window)** | -228 to -169 | Day -168 | Day -140 ±7 | Day -112 ±7 | Day -84 ±7 | Day -56 ±7 | Day -28 ±7 | Day 1 | Day 15 ±3 | Day 29 ±7 | Day 43 ±3 | Day 57 ±7 | Day 85 ±7 | Day 113 ±7 | Day 141 ±7 | | Day 169 ±7 | Day 197 ±7 | Day 225 ±7 |
| Coagulation and TG Level Pre/Post Factor or BPA Administration[l] | | X Performed at any one visit[m] | | | | | | | | | | | | | | | | | |
| Coagulation | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X |
| Nijmegen-Modified Bethesda Assay (Inhibitor Status) | X | | | | | | X | | | | | | | | | | X | X | |
| AT Activity Level[l,n] | X | | | | | | | X | X | X | X | X | X | X | X | | X | X | X |
| FVIII/FIX Levels[l] | X | | | | | | | | | | | | | | | | | | |
| Thrombophilia Screening | X | | | | | | | | | | | | | | | | | | |
| Serum Chemistry | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X |
| Liver Function Tests[o] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X |
| Antidrug Antibodies[l, n] | | | | | | | | X | | | | X | | X | | | X | X | |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X |
| Hepatic Tests[o] | X | | | | | | | X | | | | | | | | | | | |

**Table 1 - Schedule of assessments**

| | | Factor or BPA prophylaxis period[a] | | | | | | Fitusiran treatment period[b] | | | | | | | | | | AT F/U[d,e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Onset period[b] | | Efficacy period | | | | | | | | |
| **Study visit (Month)** | Screening | Month -6 | Month -5 | Month -4 | Month -3 | Month -2 | Month -1 | Baseline | | Month 1 | | Month 2 | Month 3 | Month 4 | Month 5 | EOT Month 6 | EOS/ ET[c,d] Month 7 | Month 8 |
| **Study day (±Visit Window)** | -228 to -169 | Day -168 | Day -140 ±7 | Day -112 ±7 | Day -84 ±7 | Day -56 ±7 | Day -28 ±7 | Day 1 | Day 15 ±3 | Day 29 ±7 | Day 43 ±3 | Day 57 ±7 | Day 85 ±7 | Day 113 ±7 | Day 141 ±7 | Day 169 ±7 | Day 197 ±7 | Day 225 ±7 |
| Exploratory biomarkers[l,p] (Optional) | | X | | | | | | X | | | | | X | | | | X | |
| Exploratory circulating RNA[l, p] (Optional) | | X | | | | | | X | | | | | X | | | | X | |
| Exploratory DNA sample[l] (Optional) | | X | | | | | | | | | | | | | | | | |
| Plasma PK (East Asian patients only) [l, p] | | | | | | | | X | | | | X | | X | | X | | |
| Urinalysis | X | X | | | | | | | | | | | | | | | X | |
| Urine Collection for Biomarkers[l] (Optional) | | | | | | | | X | | | | | X | | | | X | |
| HJHS[q] | | X | | | | | | X[w] | | | | | | | | | X[q] | |
| Patient Resource Use[q] | | X | | | | | | X[w] | | | | | | | | | X[q] | |

**Table 1 - Schedule of assessments**

| | | Factor or BPA prophylaxis period[a] | | | | | | Fitusiran treatment period[b] | | | | | | | | | | AT F/U[d,e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Onset period[b] | | Efficacy period | | | | | | | | |
| **Study visit (Month)** | Screening | Month -6 | Month -5 | Month -4 | Month -3 | Month -2 | Month -1 | Baseline | | Month 1 | | Month 2 | Month 3 | Month 4 | Month 5 | EOT Month 6 | EOS/ET[c,d] Month 7 | Month 8 |
| **Study day (±Visit Window)** | -228 to -169 | Day -168 | Day -140 ±7 | Day -112 ±7 | Day -84 ±7 | Day -56 ±7 | Day -28 ±7 | Day 1 | Day 15 ±3 | Day 29 ±7 | Day 43 ±3 | Day 57 ±7 | Day 85 ±7 | Day 113 ±7 | Day 141 ±7 | Day 169 ±7 | Day 197 ±7 | Day 225 ±7 |
| Haemo-QOL/Haem-A-QOL[q] | | X | | | | | | X[w] | | | | | | | | | X[q] | |
| HAL/pedHAL[q] | | X | | | | | | X[w] | | | | | | | | | X[q] | |
| TSQM-9[q] | | X | | | | | | X[w] | | | | | | | | | X[q] | |
| EQ-5D[q] | | X | | | | | | X[w] | | | | | | | | | X[q] | |
| Fitusiran Administration (Q2M) | | | | | | | | X | | | | X | | X | | X | | |
| Perioperative Assessment[r] | | | | | | | | Continuous | | | | | | | | | | |
| Patient Education Module Training | | X | | | | | | X | | | | | | | | | | |
| Bleed Management Review[s] | | Review with patient at each visit and contact every 2 weeks (±4 days) between visits | | | | | | | | | | | | | | | | |
| Bleeding Episodes/eDiary[t] | | Review with patient at each visit and contact every 2 weeks (±4 days) between visits | | | | | | | | | | | | | | | | |
| Adverse Events[u] | Continuous | | | | | | | | | | | | | | | | | |
| Concomitant Medications[v] | Continuous | | | | | | | | | | | | | | | | | |

**Table 1 - Schedule of assessments**

| | | Factor or BPA prophylaxis period[a] | | | | | | Fitusiran treatment period[b] | | | | | | | | | | AT F/U[d,e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Onset period[b] | | Efficacy period | | | | | | | | |
| **Study visit (Month)** | Screening | Month -6 | Month -5 | Month -4 | Month -3 | Month -2 | Month -1 | Baseline | | Month 1 | | Month 2 | Month 3 | Month 4 | Month 5 | EOT Month 6 | EOS/ ET[c,d] Month 7 | Month 8 |
| **Study day (±Visit Window)** | -228 to -169 | Day -168 | Day -140 ±7 | Day -112 ±7 | Day -84 ±7 | Day -56 ±7 | Day -28 ±7 | Day 1 | Day 15 ±3 | Day 29 ±7 | Day 43 ±3 | Day 57 ±7 | Day 85 ±7 | Day 113 ±7 | Day 141 ±7 | Day 169 ±7 | Day 197 ±7 | Day 225 ±7 |
| COVID-19 Testing | Anytime during the study [x] | | | | | | | | | | | | | | | | | |

Abbreviations: APRI = AST to platelet ratio; AT = antithrombin; BPA = bypassing agent; ECG = electrocardiogram; eDiary = electronic diary; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FVIII = Factor VIII; FIX = Factor IX; F/U = follow-up; HAL = Haemophilia Activities List; HJHS = Hemophilia Joint Health Score; Min = minute; pedHAL = paediatric HAL; PK = pharmacokinetics; Q2M = every 2 months; SAEs = serious adverse events; TG = thrombin generation; TSQM-9 = treatment satisfaction questionnaire for medication

Note:

- See Section 7 for study assessment instructions.
- Any Screening assessments performed within 7 days prior to Month -6 do not need to be repeated at the Month -6 visit. In exceptional circumstances, screening may be extended beyond the 60 day window after consultation with the sponsor. In this case, some assessments done at the beginning of screening may have to be repeated.
- Rescreening of patients is permitted with consultation of the study Medical Monitor.
- Laboratory parameters are described in Section 7.6.5 and listed in Table 7.
- When scheduled at the same time points, vital signs and 12-lead ECGs will be performed before the physical examinations and blood/urine sample collections.
- Unless otherwise specified, assessments on dosing days are predose.

*a* Routine prophylaxis with factor concentrates or BPAs for treatment of hemophilia. The subgroup Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in the BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. For these patients, the screening period will be from Day -60 to Day 0 and assessments during the BPA prophylaxis period are not applicable with the exception of the exploratory DNA sample. For the United States specific requirements see Section 11.6.1.1.

*b* Fitusiran as prophylaxis treatment and permitted on-demand use of factors or BPAs for treatment of breakthrough bleeding episodes. Patients may continue their routine factor or BPA administration schedule for up to the first 7 days of the onset period. For the United States specific requirements see Section 11.6.1.1.

*c* Not required at Early Termination Visit for patients who complete assessment at EOT Visit and subsequently Early Terminate.

*d* Patients who discontinue study drug dosing for any reason and agree to complete the remaining assessments through the EOS/ET and AT FU visits and may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable. For patients who withdraw from the study early and do not consent to complete remaining assessments through the EOS/ET and AT FU visits, every effort should be made to conduct the assessments performed at the EOS/ET visit.

*e* Patients not enrolling in the extension study will complete AT F/U visits at monthly intervals following final fitusiran dose until AT activity level returns to ~60% (per the central laboratory), or per Investigator discretion in consultation with the study Medical Monitor.

*f* The complete medical history/disease history (ie, including bleeding episode and treatment history over the prior 6 months) to be recorded at Screening.

*g* eDiary training will be completed at the Clinic at Screening (see Section 7.2.1).

*h* A full physical examination will be performed at Screening only; a directed physical exam will be performed at all other visits (see Section 7.6.3).

*i* Height will be recorded only at Screening for patients > 18 years old. Height for patients < 18 years old and weight for all patients will be recorded at all checked visits (Section 7.6.2).

*j* 12-lead ECGs will be performed in triplicate. On Day 1, 12-lead ECGs will be performed predose and 4 hours (±30 min) postdose (see Section 7.6.4). The Month 7 12-lead ECG will be performed only in those patients who are performing the ET visit and may be performed in singlicate.

*k* Hepatitis C virus antibody positive patients only. FibroScan where available, otherwise FibroTest and APRI.

*l* Sample may be used for study of biomarkers related to hemophilia and associated conditions, investigations of emerging safety issues, or the development of fitusiran. After specified analyses are run, residual samples may be stored for up to 15 years from last patient, last visit, or as per local regulations, and used for further study of biomarkers related to hemophilia and associated conditions, investigation of emerging safety issues, or the development of fitusiran. Samples drawn from central lines may be excluded from TG analysis.

*m* To be performed in all patients, at any clinic visit during their factor or BPA prophylaxis period, with blood drawn before, 10 min (±5 min) after, and 60 min (±5 min) after administration of their usual prophylactic dose of factor or BPA. Laboratory testing pre- and post- factor/BPA include: Coagulation, and TG. The timing of this visit should coincide with the patient's usual prophylaxis regimen, so that pre-dose thrombin generation is at nadir and the benefit of administered factor or BPA is maintained. For the United States specific requirements see Section 11.6.1.1.

*n* On fitusiran dosing days, samples will be collected within 4 hour priors to dosing. For the AT assessments, upon the first AT level <15%, the patients must have another AT activity level sample drawn within 1 week of site receipt of the results.

*o* Liver function tests (LFTs) and hepatic tests are as listed in Table 7. LFTs may be obtained up to 7 days before the clinic visit on which fitusiran dosing is scheduled. LFTs performed within 7 days of Day 1 will only be used to inform dosing on Day 1 and do not need to be used to confirm eligibility. LFTs can be analyzed locally, but if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory. Under conditions of elevated ALT and/or AST, see Section 6.2.3.1 and Table 8. LFT results will be obtained prior to receiving monthly fitusiran dosing.

*p* Blood samples for PK analysis will be collected at the time points listed in Table 11 in East Asian patients at East Asian sites.

*q* Must be completed at clinic. Will be collected at EOS visit; not collected at ET visit.

*r* Perioperative assessment of safety and hemostatic efficacy only in patients undergoing major operative procedures while on study drug (see Table 12).

*s* Will include review of entries, (symptoms of bleed events, bleed causality, bleed severity, doses administered), whether appropriate site contact occurred regarding treatment of bleeds, and review of patient bleed management plan and recommendations and requirements for site contact regarding dosing.

*t* It is strongly preferred that factor or BPA administration and bleeding events are entered in the eDiary immediately or within 24 hours. Additional patient follow-up may be required as described in Section 7.2.1. Patients in the fitusiran treatment arm who present in the clinic with symptoms characteristic of a potential bleeding episode should have assessments completed per Table 2. For the United States specific requirements see Section 11.6.1.1.

*u* AEs will be monitored and recorded from date of signed informed consent through Follow-Up. Signs and symptoms of thrombosis will be evaluated at every visit (see Section 6.5).

*v* In addition to recording concomitant medications, documented history of prior medications will be collected during Screening.

*w* As per patient and Investigator convenience, these assessments can be completed on a different day within 2 days prior to the Baseline visit.

*x* All study patients that are consenting to this procedure are requested to undergo testing for SARS-CoV-2 (virus responsible for COVID-19), which should include both RT-PCR and antibody testing. These tests should be performed as early as possible during the study. Alternatively, historical test results may be provided under certain circumstances as defined by Sponsor.

**Table 2 - Bleeding episode assessments - unscheduled visit**

| | Predose | Postdose 10 min (±5 min)[d] | Postdose 60 min (±5 min) [d] |
|---|---|---|---|
| Directed Physical Examination[a] | X | | |
| Vital Signs | X | | |
| AT | X | | |
| FVIII/FIX Levels (only if treated with FVIII or FIX) | X | X | X |
| TG | X | X | X |
| Coagulation | X | X | X |
| Hematology | X | X | X |
| Optional Imaging[c] | X | | |

Abbreviations: AT = antithrombin; FVIII = Factor VIII; FIX = Factor IX; TG = thrombin generation

For the United States specific requirements see Section 11.6.1.1.

*a* See Section 7.6.3 for assessments to be performed during a directed physical examination.

*b* Removed.

*c* Investigator to consider confirmation of bleed via ultrasound or other imaging modality at clinical study centers where appropriate equipment and staff with related expertise is available.

*d* If the patient presents following administration of factor or BPAs at home and within 48 hours of the dose, and no further treatment is given at the center, AT and the postdose assessments should be obtained in a single draw at any time during the visit.

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ABR | annualized bleeding rate |
| AE | adverse event |
| ALT | alanine transaminase |
| aPCC | activated prothrombin complex concentrates |
| APRI | AST to platelet ratio index |
| AST | aspartate transaminase |
| AT | antithrombin |
| AUC | area under the concentration-time curve |
| BPA | bypassing agent |
| CFR | Code of Federal Regulation |
| CL/F | apparent clearance |
| $C_{max}$ | maximum plasma concentration |
| COVID-19 | Coronavirus Disease 2019 |
| CYP P450 | cytochrome P450 |
| DMC | Data Monitoring Committee |
| DTP | Direct-to-Patient |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eDiary | electronic diary |
| EOS | end of study |
| EOT | end of treatment |
| EQ-5D | EuroQol- 5 dimension |
| FIX | Factor IX |
| FV | Factor V |
| FVIII | Factor VIII |
| FX | Factor X |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| HAL | Haemophilia Activities List |
| Haem-A-QOL | Haemophilia Quality of Life Questionnaire for Adults |
| Haemo-QOL | Haemophilia Quality of Life Questionnaire for Children and Adolescents |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| HRQOL | health-related quality of life |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal product |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| ISR | injection site reaction |
| ISTH | International Society on Thrombosis and Haemostasis |
| IV | intravenously |
| MAD | multiple-ascending dose |
| MD | multiple dose |
| mRNA | messenger ribonucleic acid |
| NHP | non-human primates |
| NOAEL | no observed adverse effect level |
| OTC | over-the-counter |
| pedHAL | pediatric HAL |
| PK | pharmacokinetics |
| PT | prothrombin time |
| Q2M | every 2 months |
| QM | every month |
| QOL | quality of life |
| RT-PCR | reverse transcription polymerase chain reaction |
| rVIIa | recombinant Factor VIIa |
| SAD | single-ascending dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SC | subcutaneous |
| SDay | surgery day |
| siRNA | small interfering ribonucleic acid |
| $t_{max}$ | time to maximum plasma concentration |
| TG | thrombin generation |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| TSQM | Treatment Satisfaction Questionnaire for Medication |
| $t_{½\beta}$ | elimination half-life |
| ULN | upper limit of normal |
| V/F | apparent volume of distribution |

# 1 INTRODUCTION

## 1.1 DISEASE OVERVIEW

Hemophilia A and hemophilia B are X-linked recessive inherited bleeding disorders, characterized by deficiency of coagulation Factors VIII (FVIII) or Factor IX (FIX), leading to a profound defect of thrombin generation with impaired hemostasis and increased risk of bleeding. Hemophilia A is found in approximately 1 in 4000 males whereas hemophilia B is five times less common and seen in approximately 1 in 20,000 males (1). The disease affects all ethnicities and the mutation responsible for hemophilia is typically inherited from a carrier parent, although spontaneous mutations are responsible for ~30% of all cases (2).

The disease phenotype presents similarly in hemophilia A and B (3). Hemophilia is classified as mild (factor levels 6% to 30%), moderate (factor levels 1% to 5%), or severe (factor levels <1%) based on clotting factor activity relative to normal (healthy, non-hemophiliac plasma levels of factor are 50% to 150%). Patients with mild hemophilia typically experience bleeding after a serious injury or surgery; patients with moderate hemophilia experience bleeding episodes associated with injuries, and may have spontaneous bleeding episodes; severe hemophilia patients experience substantial bleeding with injury and may have frequent spontaneous bleeding episodes resulting in debilitating musculoskeletal damage that can markedly impair a patient's mobility and quality of life (QOL).

The hemostatic system aims to maintain the integrity of the vasculature by protecting against bleeding from vessel lesions combined with multiple options to prevent thrombosis. This hemostatic balance is achieved through an orchestrated regulation of both procoagulant (eg, Factor V [FV], Factor VII [FVII], FVIII, FIX, Factor X [FX]) and anticoagulant (eg, antithrombin, protein C/protein S and tissue factor pathway inhibitor) factors. Recent studies have suggested that coinheritance of a deficiency in natural anticoagulants may contribute to a milder phenotype in patients with hemophilia. Antithrombin (AT) is a liver-expressed natural anticoagulant that plays a key role in inhibiting thrombin. Furthermore, AT acts as an inhibitor of FVIIa and FXa, which are typically at normal levels in patients with hemophilia A or B. Extensive preclinical in vitro and in vivo studies have described reduction of AT as a potential safe and effective way to correct thrombin generation in both hemophilia A and B and control against microvascular and macrovascular traumatic bleeding episodes (4). Therefore, suppression of AT production is being investigated as a potential hemophilia treatment.

Replacement with factor concentrates is the current standard of care for hemophilia patients without inhibitory antibodies to FVIII or FIX. While the current standard of care of factor substitution therapy, administered either episodically or as routine prophylaxis, is well established, safe, and efficacious, it is associated with high treatment burden due to requiring intravenous (IV) administration on a frequent schedule (2 to 3 times per week or more) to prophylactically maintain hemostasis (3). Factor concentrates also can be of limited availability in developing nations. In addition, patients receiving factor concentrates may develop an inhibitory antibody to factor, a result that carries a poorer prognosis and requires a change in treatment regimen to infusion with BPAs.

Hemophilia patients who develop inhibitory antibodies to factor concentrates represent a distinct subset of the population; these patients typically experience more difficult-to-treat bleeding episodes, leading to increased morbidity and increased mortality (5). Development of inhibitors to infused factor occurs mainly in severe hemophilia, and more frequently in hemophilia A (up to 39% of patients) (6, 7) than in hemophilia B (1% to 3.5% of patients) (8, 9) with the greatest risk of development in the early exposure days. These "inhibitor" patients, may be eligible for immune tolerance therapy, however in most cases bleeding episodes require hemostatic intervention with intravenously (IV)-administered BPAs, ie, recombinant Factor VIIa (rVIIa), or activated prothrombin complex concentrates (aPCC), either as prophylaxis or as on-demand episodic treatment of bleeding episodes.

A subcutaneous therapy that can effectively and safely prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B, including those with inhibitors, may reduce treatment burden, improve clinical outcomes and enhance quality of life. Fitusiran is being developed to address these needs of patients with hemophilia.

## 1.2 FITUSIRAN (SAR439774)

Fitusiran (SAR439774 [formerly Alnylam ALN-AT3SC]) is an investigational agent comprising a synthetic siRNA covalently linked to a triantennary GalNAc ligand, designed to suppress liver production of AT as a strategy to rebalance the hemostatic system, thereby improving thrombin generation and hemostasis in individuals with hemophilia.

Fitusiran is a GalNAc-siRNA conjugate that reduces production of AT, leading to lower plasma AT levels. By reducing plasma AT, fitusiran is designed to improve thrombin generation and hemostasis in individuals with hemophilia, regardless of hemophilia type or presence of inhibitory antibodies to Factor VIII or IX. Because of the durability of the PD effect of fitusiran demonstrated in previous nonclinical and clinical studies, the subcutaneous (SC) administration required is notably less frequent than current IV standard of care with factor concentrates or BPAs (as frequent as every other day in severe cases), representing potentially improved quality of life and lowered treatment burden for patients with hemophilia. Further, with the durable PD effect, it is possible that fitusiran may maintain a patient at a more consistent, robust hemostasis than intermittent factor concentrates or BPAs.

Fitusiran is being developed for the indication of routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B with or without inhibitory antibodies to FVIII or FIX.

### 1.2.1 Summary of nonclinical data with fitusiran

Nonclinical pharmacology and exploratory toxicity studies have been conducted in wild-type (WT) and hemophilia mouse models, as well as WT rats, WT dogs, hemophilic dogs, and WT non-human primates (NHP). The fitusiran siRNA sequence is homologous across all tested species; therefore, across multiple studies (single and repeat-dose), fitusiran exhibits potent and dose-dependent pharmacologic activity, resulting in reduced tissue AT mRNA levels and subsequent reduced circulating AT protein and activity levels, with a single-dose ED50 of

~1 mg/kg in multiple species. Exploratory pharmacology studies have also been completed in the hemophilia A dog and in an NHP induced hemophilia model.

A GLP-compliant SC safety pharmacology study in NHP was conducted and there were no effects on measured cardiovascular or respiratory parameters after a single SC dose at any dose, with a NOEL for cardiovascular effects of [redacted] (highest dose evaluated). There were no neurological effects in the GLP 39-week NHP study with a NOEL of [redacted] (highest dose evaluated with repeat dosing). The pharmacology studies are summarized in greater detail in the Investigator's Brochure.

Plasma PK and toxicokinetic studies of single and repeated IV and/or SC [redacted] doses of fitusiran were conducted in rats, dogs, and monkeys, and [redacted] of fitusiran in mice. Following SC administration, fitusiran was rapidly absorbed following IV and SC administrations of [redacted] in mice with $C_{max}$ occurring within 30 minutes of dose administration followed by clearance in a biphasic manner. There were no gender-related differences in the PK properties of fitusiran. After repeat dosing, the plasma PK profiles were similar after first and last dose indicating no time dependent changes in the PK of fitusiran.

In the in vitro studies of rats and NHPs fitusiran did not cause induction of the common P450 isoforms and was not a substrate for the common cytochrome P450 (CYP P450) isoforms.

Genetic toxicity studies (bacterial reverse mutation, mammalian chromosome aberration, rat micronucleus test) have been completed, and demonstrated that fitusiran is non-genotoxic. GLP toxicology (7-weekly doses) studies were conducted with fitusiran in the rat and NHP. A chronic 26-week study in the rat and a 39-week study in NHP have been completed. The no observed adverse effect level (NOAEL) in the 7-week rat toxicology study was [redacted], and in the 26-week rat toxicology study was [redacted]. The NOAEL in the 7-week NHP study was [redacted], and the NOAEL in the chronic NHP study was [redacted]. The NOAELs in all studies were based on toxicity attributable to the exaggerated on-target, pro-coagulant pharmacology of fitusiran that is expected in wild type animals (hemorrhage and/or thrombosis in various tissues, which led to mortality above a threshold of approximately [redacted]). By contrast, in exploratory studies, highly exaggerated doses of fitusiran (exposures in 100-fold excess of therapeutic relevance; >95% reduction in AT) were well tolerated in hemophilia A and B mice, with no evidence of toxicity or thrombosis. A 26-week GLP chronic toxicity in the hemophilia A mouse model was conducted. The top dose of [redacted] was well tolerated for 26 weeks, indicating that hemophilic animals are not predisposed to pro-thrombotic effects compared to WT animals; a survival benefit was demonstrated in animals dosed with fitusiran vs saline controls (40% mortality in saline control vs 6% in fitusiran treated groups [$p<0.0001$ by Log-Rank test]). In addition, 6-month TgRasH2 mouse and 2-year rat carcinogenicity studies are currently ongoing.

In the GLP-compliant 39-week chronic NHP toxicology study, administration of fitusiran by once weekly SC injection to peripubertal cynomolgus monkeys at doses of [redacted] was well tolerated (approximately 70% chronic AT suppression at [redacted]). Based on the absence of fitusiran related effects on the toxicology parameters evaluated at all dose levels tested, the NOAEL was considered to be [redacted].

There was no effect of fitusiran on male reproduction in the rat and with repeat dose administration of fitusiran to juvenile rats and sexually immature cynomolgus monkeys, growth and maturation were unaffected. Overall, fitusiran was well tolerated locally, and non-genotoxic. Fitusiran does not activate the immune system.

Taken together, the results from the nonclinical studies exhibit reduction in AT activity level, increase in thrombin generation, and corrective effect on hemostasis, thereby validating the therapeutic approach of the clinical studies. These nonclinical studies are summarized in the Investigator's Brochure.

### 1.2.2 Summary of clinical data with fitusiran

The Investigator must become familiar with all sections of the fitusiran Investigator's Brochure which will be provided by the Sponsor before the start of the study and during the study, as amendments are completed.

Details of completed and ongoing studies of fitusiran are presented in the Investigator's Brochure.

#### *1.2.2.1 Summary of efficacy*

In Phase 1/2 clinical trials, monthly dosing with fitusiran in patients with hemophilia A and B, with or without inhibitors, resulted in sustained antithrombin lowering and improved hemostasis as measured by reductions in patients' annualized bleeding rate (ABR) (10, 11).

A complete summary of available clinical efficacy data relevant to fitusiran is presented in the Investigator's Brochure.

#### *1.2.2.2 Summary of safety*

Events of serious vascular thrombosis, liver transaminase abnormalities, cholecystitis, and symptomatic cholelithiasis have been reported in the clinical development program and are considered identified risks of fitusiran. In addition, serious hypersensitivity reactions, including injection site reactions, are considered a potential risk of fitusiran.

One death has been reported in a patient with cerebral venous thrombosis (CVST) in ALN-AT3SC-002. In response to this event, the bleed management guidelines were revised in December 2017.

A more detailed summary of available clinical safety data is presented in the Investigator's Brochure.

#### *1.2.2.3 Summary of pharmacokinetic and pharmacodynamic effects in ALN-AT3SC-001 and ALN-AT3SC-002*

Consistent with the intended pharmacological effects, regardless of inhibitor status, fitusiran dose-related reductions in AT activity level have been observed in the clinical studies and have been associated with increased thrombin generation. In Part C of the Phase 1 study, the mean maximum AT activity level reductions following 3 monthly doses of 0.225, 0.45, 0.9 or 1.8 mg/kg fitusiran were 70% (N=3), 77% (N=3), 77% (N=3), and 89% (N=3), respectively. A fixed dose, 80 mg fitusiran, was also explored in Part C, resulting in a mean maximum AT activity level reduction of 87% (N=6). In Part D of the study, patients with inhibitors were dosed with 50 or 80 mg fitusiran and experienced mean maximum AT activity level reduction of 82% (N=6) and 87% (N=10), respectively. AT reduction was maintained in ALN-AT3SC-002, with mean maximal AT reduction of 83.6% for 50 mg (N=13) and 85.9% for 80 mg (N=21) as of 08 August 2017.

Consistent with the therapeutic hypothesis, increased AT lowering in patients with hemophilia resulted in increased thrombin generation when AT lowering was in the highest quartile (>75%) compared to when AT lowering was in the lowest quartile (<25%). Further, the peak thrombin generation values achieved with AT lowering of >75% were comparable to those in the lower end of the normal range observed in healthy individuals. None of the thrombin generation measurements following >75% AT reduction in hemophilia patients exceeded those seen in healthy males.

## 1.3 STUDY DESIGN RATIONALE

The ATLAS-PPX trial (Alnylam ALN-AT3SC-009 [Sanofi Genzyme EFC15110]) is a multicenter, multinational, open-label Phase 3 switching study designed to demonstrate the efficacy and safety of fitusiran in patients with hemophilia A or B, who are currently treated with prophylactic regimens of factor concentrates or BPAs.

The switching design allows for an intra-patient control to enable examination of the effect of the two treatment methods through comparison of the median ABR during the factor or BPA prophylaxis period and the median ABR of the same patient group when receiving fitusiran, while limiting confounding effects of different patient bleeding phenotypes and prophylaxis therapy variability. Inhibitor patients with hemophilia B may have a high unmet need despite prophylactic BPA therapy, with limited other treatment options. Therefore, a limited number of inhibitor patients with hemophilia B who are not adequately responding to prophylactic BPA therapy could enroll directly into the fitusiran treatment period, thereby skipping the 6-month BPA prophylaxis period. 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. For the United States specific requirements, see Section 11.6.1.2.

Given that the study design employed is a single treatment arm, with a switch from prophylaxis to fitusiran for each patient, the study is not blinded.

The primary endpoint of the study is ABR in the fitusiran efficacy period and the factor or BPA prophylaxis period. ABR is a well-established endpoint that has been used as the primary endpoint in global approvals of factor replacement and BPA products. Secondary endpoints characterize annualized spontaneous and joint bleeding rates, change in Haem-A-QoL physical health score and total score in patients ≥17 years of age, ABR in the onset period, overall safety profile and the consumption of factor/BPA.

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, has been used in other hemophilia clinical trials, has been validated, reviewed by clinicians, and is considered the most appropriate HRQOL tool available for use in the 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 (12).

In the event of a breakthrough bleeding episode, on-demand use of factors or BPAs will be permitted throughout the entire study duration (see Section 6.3.2).

## 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 using both observed data from ongoing clinical studies, as well as extensive clinical simulations and modeling. The key pharmacodynamic (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 pharmacokinetic/pharmacodynamic (PK/PD)-modeled data, supported the initial 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 was 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 suggested that the maximum AT lowering achieved as a function of the dose administered reached an asymptote at ~90% AT lowering and that it was 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 approached the lower end of the normal range, but did 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 was anticipated to result in near 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.

A change in the fitusiran dosing regimen is being introduced as a risk mitigation measure for vascular thrombotic events. As the risk of vascular thrombotic events is thought to be increased in the setting of low AT activity levels, a reduced dose of 50 mg administered SC once every 2 months has been selected to minimize the occurrence of AT activity levels below 10%. At a reduced dose of 50 mg every 2 months, if a patient has more than 1 AT activity level <15% at any time during fitusiran treatment, the patient will be required to permanently discontinue fitusiran.

**Dosing Regimen Simulation**

A PK/PD model that describes the dynamics of AT activity for patients treated with fitusiran was developed and characterized on AT activity data from Phase 1 and Phase 2 studies. The model with the estimated parameters was used to simulate AT activity at steady state for different dosing scenarios in a virtual population of 1000 patients.

The results of the simulations are shown in Table 3. Every 2 months (Q2M) and every month (QM) refer to fitusiran dosing every 8 weeks and every 4 weeks respectively; Trough AT and Peak AT are trough and peak AT activities; 5th, Median and 95th referring to 5th percentile, median and 95th percentile.

**Table 3 – Simulated AT activity percentiles, for various doses of fitusiran**

| REGIMEN | Min AT | TroughAT_5th_SS | TroughAT_Median_SS | TroughAT_95th_SS | Max AT | PeakAT_5th_SS | PeakAT_Median_SS | PeakAT_95th_SS |
|---|---|---|---|---|---|---|---|---|
| 50 Q2M | 10.5 | 13.9 | 23.3 | 39.7 | 77.5 | 17.87 | 32.37 | 56.42 |
| 50 QM | 7.96 | 10.3 | 17.2 | 29.6 | 58.5 | 11.36 | 18.23 | 31.15 |

Based on the simulation results from Table 3, starting all patients on a 50 mg Q2M regimen is expected to achieve AT activity above 10% for all patients.

## 1.5 BENEFIT-RISK ASSESSMENT

Based on the available clinical data (see Section 1.2.2), fitusiran 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.

Identified risks of fitusiran include serious vascular thrombosis, liver transaminase abnormalities, cholecystitis, and symptomatic cholelithiasis. In addition, serious hypersensitivity reactions, including injection site reactions, are considered a potential risk of fitusiran. The risk of vascular thrombotic events is thought to be elevated in patients receiving fitusiran with AT activity levels <10%. In addition, the concomitant treatment of breakthrough bleeding episodes with factor or BPA, due to particularly at doses higher than recommended in the protocol may confer an increased risk of thrombotic events. Additional details regarding the benefits and risks of fitusiran are provided 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 a change in the fitusiran dosing regimen to minimize the occurrence of AT levels <10% (Section 6.2.3.2), detailed guidance and oversight on treatment of breakthrough bleeding episodes with reduced factor and/or BPA dosing (Section 6.3.2), and monitoring and management of thrombosis while patients are on fitusiran (Section 6.5). 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).

For the United States specific requirements, see Section 11.6.1.2.

# 2 OBJECTIVES

## 2.1 PRIMARY OBJECTIVE

- To characterize the frequency of bleeding episodes while receiving fitusiran treatment, relative to the frequency of bleeding episodes while receiving factor concentrate or bypassing agent (BPA) prophylaxis. For the United States specific requirements, see Section 11.6.1.2.

## 2.2 SECONDARY OBJECTIVES

- To characterize the following while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis (for the United States specific requirements, see Section 11.6.1.2):
  - 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 characterize the frequency of bleeding episodes during the onset and treatment periods in patients receiving fitusiran
- To characterize safety and tolerability of fitusiran
- To characterize the annualized weight-adjusted consumption of factor/BPA while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis

## 2.3 EXPLORATORY OBJECTIVES

- To characterize the effects of fitusiran on the following patient-reported outcomes while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis (for the United States specific requirements, see Section 11.6.1.2):
  - Patient satisfaction with fitusiran
  - Patient activity
  - HRQOL in adolescents (≥12 to <17 years of age)
- To characterize the pharmacodynamic (PD) effect, PK, and immunogenicity of fitusiran
- To characterize the effects of fitusiran on joint status while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis
- To characterize the effects of fitusiran on patient resource use, relative to receiving factor or BPA prophylaxis

# 3 ENDPOINTS

## 3.1 PRIMARY ENDPOINT

- Annualized Bleeding Rate (ABR) in the fitusiran efficacy period and the factor or BPA prophylaxis period (for the United States specific requirements, see Section 11.6.1.2)

## 3.2 SECONDARY ENDPOINTS

- Annualized spontaneous bleeding rate in the fitusiran efficacy period and the factor or BPA prophylaxis period (for the United States specific requirements, see Section 11.6.1.2)
- Annualized joint bleeding rate in the fitusiran efficacy period and the factor or BPA prophylaxis period (for the United States specific requirements, see Section 11.6.1.2)
- Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period
- ABR in the onset period
- ABR in treatment period
- Annualized weight-adjusted consumption of factor/BPA

## 3.3 EXPLORATORY ENDPOINTS

- Change in the following in the fitusiran treatment period:
  - Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores
  - Haemophilia Activities List (HAL) score
  - Paediatric HAL (pedHAL) score
  - EuroQol-5 Dimensions (EQ-5D) score
  - 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 period
- AT activity level over time
- Thrombin generation over time
- Fitusiran plasma levels
- 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

# 4 INVESTIGATIONAL PLAN

## 4.1 SUMMARY OF STUDY DESIGN

The ATLAS-PPX trial (ALN-AT3SC-009) is a multicenter, multinational, open-label, Phase 3 study designed to characterize the efficacy and safety of fitusiran in male patients, aged ≥12 years, with severe hemophilia A or B, previously receiving factor or BPA prophylaxis. The study consists of 2 cohorts: Cohort A will consist of patients with inhibitory antibodies to Factor VIII or Factor IX; Cohort B will consist of patients without inhibitor antibodies to Factor VIII or Factor IX. A subgroup of Cohort A patients will include hemophilia B patients with inhibitory antibodies to Factor IX who are not responding adequately to BPA prophylaxis treatment (historical ABR ≥20) (see Inclusion Criteria in Section 5.1). The study has 3 periods defined by type of prophylaxis regimen (for the United States specific requirements, see Section 11.6.1.2):

- 6-Month factor or BPA prophylaxis period in which patients will continue their prestudy, regularly scheduled prophylaxis regimen with factors or BPAs

  The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this 6-Month BPA prophylaxis period and will start to directly receive fitusiran (in the 1-month onset period described below) after the screening period.

- 1-Month onset period in which patients receive first dose of fitusiran while continuing their factor or BPA prophylaxis for up to 7 days

- 6-Month fitusiran efficacy period in which patients receive fitusiran as prophylaxis.

Together, the 1-month onset period and the 6-month fitusiran efficacy period constitute the fitusiran treatment period.

Bleeding events and doses of factor concentrates or BPAs 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 7.6.6.1. Safety, quality of life, pharmacodynamic, and pharmacokinetic data will also be collected.

On-demand use of factor concentrates or 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 period may receive on-demand treatment for breakthrough bleeding episodes with factors or BPAs, as appropriate. For patients in the fitusiran treatment period 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 6.3.2 per Investigator discretion.

Following the screening and prophylaxis periods or following the screening period for the subgroup of Cohort A enrolling directly into the fitusiran treatment period all patients will be treated with fitusiran for a total of 7 months. Therefore, the overall fitusiran treatment period is

defined as the onset period (Day 1-28 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). For the United States specific requirements, see Section 11.6.1.2.

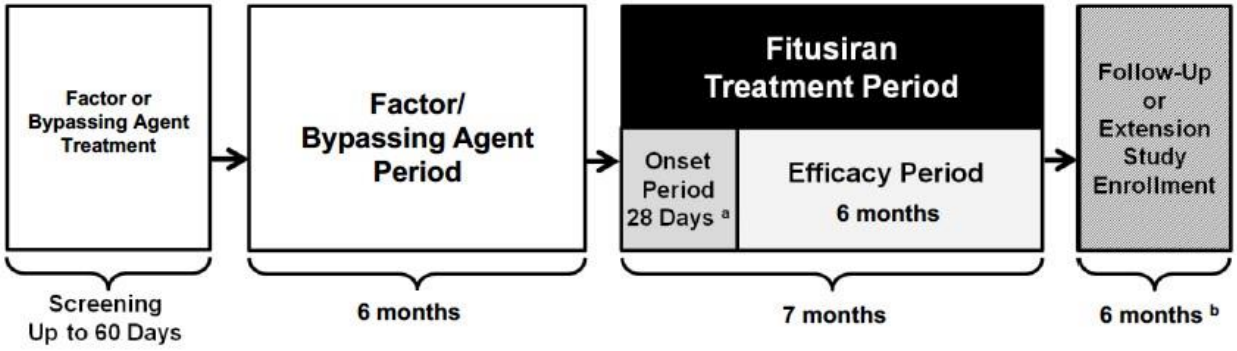
Any current surgery occurring close to the date of the Screening visit must have surgery-related hemostatic treatment completed at least 72 hours prior to Screening. Patients may undergo unplanned or emergency surgery during the study but must not schedule non-urgent surgery to occur during the study. 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.

**Figure 1 - Study design**



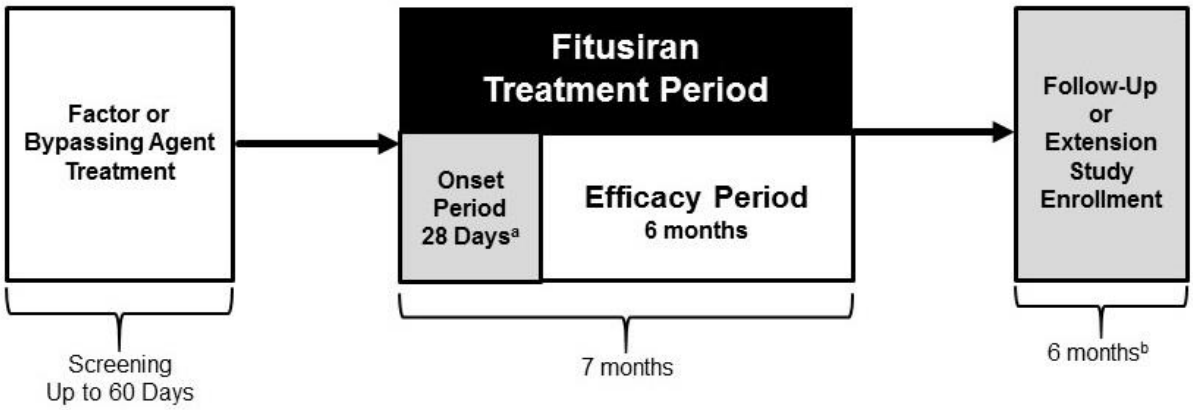

Abbreviations: AT=antithrombin
Note: For subgroup of Cohort A patients enrolling directly into the fitusiran treatment period, see Figure 2.

Note: For the United States specific requirements, see Section 11.6.1.2.

*a* Patients will continue to receive prescribed factor or BPA prophylaxis for the first 7 days of the onset period.

*b* Following final fitusiran dose, 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.

**Figure 2 - Study design (for subgroup of Cohort A patients enrolling directly into the fitusiran treatment period)**




Abbreviations: AT=antithrombin

Note: For the United States specific requirements, see Section 11.6.1.2.

*a* Patients will receive prescribed factor or BPA prophylaxis for the first 7 days of the onset period.

*b* Following final fitusiran dose, 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 7 months. The estimated total time on the study, inclusive of screening, for each patient is up to 15 months for all patients who enroll in the extension study, except for patients in the subgroup of Cohort A, which is up to 9 months. The estimated total time on study may be up to 21 months (up to 15 months for patients in the subgroup of Cohort A) for 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 80 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 50 patients without inhibitors (Cohort B). Approximately 18 patients with hemophilia B (including approximately 7 hemophilia B patients in Cohort A, among which are a subgroup of no more than 4 patients who are not responding adequately to BPA prophylaxis [see Section 5.1]), approximately 11 hemophilia B patients in Cohort B, and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment. For the United States specific requirements, see Section 11.6.1.2.

## 4.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

All patients will be assigned to the same treatment sequence (prophylaxis period followed by fitusiran period) in this open-label study.

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.

## 4.5 BLINDING

This study is an open-label study so blinding is not applicable; however, performing aggregate summaries of efficacy data will be restricted until database lock.

## 4.6 STUDY STEERING COMMITTEE

A study Steering Committee, composed of experts in the field of hemophilia, will advise the Sponsor on study design and conduct. In collaboration with the Sponsor, the committee will provide scientific leadership to the study to ensure that the highest standards are maintained.

Clinical Advisors who are experts in the care of hemophilia patients and familiar with fitusiran will be available to discuss clinical aspects of care with Investigators for surgical cases, cases of thrombosis, or other medically complex circumstances that may arise on study, when clinical circumstances allow. Such discussions will also look to involve the study Medical Monitor.

## 4.7 DATA MONITORING COMMITTEE

An independent DMC will oversee the safety and overall conduct of this study, providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC has the responsibility for reviewing safety data and analyses and making recommendations to the Sponsor. 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.

# 5 SELECTION AND WITHDRAWAL OF PATIENTS

## 5.1 INCLUSION CRITERIA

Each patient must meet all of the following inclusion criteria to be eligible for enrollment in the study (for the United States specific requirements, see Section 11.6.1.2):

I 01. Males ≥12 years of age.

I 02. Severe hemophilia A or B as evidenced by:

a) A central laboratory measurement at screening or documented medical record evidence of FVIII <1% or FIX level ≤2%.

I 03. A minimum of 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening for patients with inhibitory antibodies to Factor VIII or Factor IX (Cohort A). A minimum of 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening for patients without inhibitory antibodies to Factor VIII or Factor IX (Cohort B).

I 04. Must meet either the definition of inhibitor or non-inhibitor patient as below:

Inhibitor:

Use of BPAs for prophylaxis and for any bleeding episodes for at least the last 6 months prior to Screening, and meet one of the following Nijmegen-modified Bethesda assay results criteria:

- Inhibitor titer of ≥0.6 BU/mL at Screening, or
- Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of 2 consecutive titers ≥0.6 BU/mL, or
- Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of anamnestic response
- The subgroup of patients in Cohort A patients must additionally meet the following criteria to be eligible to start treatment with fitusiran directly after the screening period:
  - Hemophilia B with inhibitory antibody to Factor IX as defined above
  - Not responding adequately to BPA treatment (historical ABR ≥20) prior to enrollment
  - In the opinion of the Investigator, with approval of Sponsor Medical Monitor, 6-month BPA prophylaxis period should be omitted.

Non-inhibitor:

Use of factor concentrates for prophylaxis and for any bleeding episodes for at least the last 6 months prior to Screening, and meet each of the following criterion:

- Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening and
- No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening and
- No history of immune tolerance induction therapy within the past 3 years prior to Screening.

I 05. Prescribed prophylactic treatment (documented in the medical or pharmacy records) of hemophilia with factor concentrates or BPAs for at least 6 months prior to Screening; the regimen must be consistent with the approved prescribing information for the product or local recommendations, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding.

I 06. Adherent to the prescribed prophylactic therapy for at least 6 months prior to Screening per Investigator assessment.

I 07. Willing and able to comply with the study requirements and to provide written informed consent and assent in the case of patients under the age of legal consent, per local and national requirements.

## 5.2 EXCLUSION CRITERIA

Each patient must not meet any of the following exclusion criteria to be eligible for enrollment in the study (for the United States specific requirements, see Section 11.6.1.2):

E 01. Known co-existing bleeding disorders other than hemophilia A or B, ie, Von Willebrand's disease, additional factor deficiencies, or platelet disorders.

E 02. Current participation in immune tolerance induction therapy (ITI).

E 03. AT activity <60% at Screening, as determined by central laboratory measurement.

E 04. Presence of clinically significant liver disease, or as indicated by any of the conditions below:

a) INR >1.2;
b) ALT and/or AST >1.5× upper limit of normal reference range (ULN);
c) Total bilirubin >ULN (>1.5× ULN in patients with Gilbert's Syndrome);
d) History of portal hypertension, esophageal varices, or hepatic encephalopathy;
e) Presence of ascites by physical exam.

E 05. Hepatitis C virus antibody positive, except patients with a history of HCV infection who meet both conditions a. and b.:

a) Completed curative treatment at least 12 weeks prior to enrollment and attained sustained virologic response as documented by a negative HCV RNA at screening, or they have spontaneously cleared infection as documented by negative HCV RNA at Screening.

b) No evidence of cirrhosis according to one of the following assessments:

- FibroScan <12.5 kPa (where available), or
- FibroTest score <0.75 and APRI <2 (if FibroScan unavailable)

E 06. Presence of acute hepatitis, ie, hepatitis A, hepatitis E.

E 07. Presence of acute or chronic hepatitis B infection (IgM anti-HBc antibody positive or HBsAg positive).

E 08. Platelet count ≤100,000/μL.

E 09. Presence of acute infection at Screening.

E 10. Known to be HIV positive with CD4 count <200 cells/μL.

E 11. Estimated glomerular filtration rate ≤45 mL/min/1.73 $m^2$ (using the Modification of Diet in Renal Disease [MDRD] formula).

E 12. Co-existing thrombophilic disorder, as determined by presence of any of the below as identified at central laboratory (or via historical results, where available):

a) FV Leiden mutation (homozygous or heterozygous)

b) Protein S deficiency

c) Protein C deficiency

d) Prothrombin mutation (G20210A; homozygous and heterozygous)

E 13. History of antiphospholipid antibody syndrome.

E 14. History of arterial or venous thromboembolism, atrial fibrillation, significant valvular disease, myocardial infarction, angina, transient ischemic attack, or stroke. Patients who have experienced thrombosis associated with indwelling venous access may be enrolled.

E 15. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin that has been successfully treated.

E 16. Any condition (eg, medical concern), which in the opinion of the Investigator, would make the patient unsuitable for dosing on Day 1 or which could interfere with the study compliance, the patient's safety and/or the patient's participation in the completion of the treatment period of the study. This includes significant active and poorly controlled

(unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to hemophilia identified by key laboratory abnormalities or medical history.

E 17. At Screening, anticipated need of surgery during the study or planned surgery scheduled to occur during the study.

E 18. Completion of a surgical procedure within 14 days prior to Screening, or currently receiving additional factor concentrate or BPA infusion for postoperative hemostasis.

E 19. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.

E 20. Inadequate venous access, as determined by the Investigator, to allow the blood draws required by the study protocol.

E 21. History of intolerance to SC injection(s).

E 22. Current or future participation in another clinical study, scheduled to occur during this study, involving an investigational product other than fitusiran or an investigational device; in order to participate in this study, patient must discontinue the investigational product or investigational device at least 30 days (or 5× the investigational product half-life, whichever is longer) prior to dosing (Day 1).

E 23. Current or prior participation in a gene therapy trial.

E 24. History of alcohol abuse within the 12 months before Screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).

## 5.3 REMOVAL FROM THERAPY OR ASSESSMENT

Patients or their legal guardian (in case patient is a minor) are free to discontinue treatment or withdraw from the study at any time and for any reason, without penalty to their continuing medical care. Any discontinuation of treatment or withdrawal from the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator. The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest.

Patients who discontinue their prophylactic treatment or withdraw consent during the factor or BPA prophylaxis period (BPA prophylaxis period is not applicable for the subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment) will be withdrawn from the study. For the United States specific requirements, see Section 11.6.1.2.

Procedures for discontinuation of study drug and/or withdrawal from the study during the fitusiran treatment period are described in Section 5.3.1 and Section 5.3.2, respectively.

### 5.3.1 Discontinuation of study drug

The Investigator or designee may discontinue dosing in a patient if the patient:

- Is in significant violation of the protocol
- Is non-adherent to treatment regimen
- Experiences a serious or intolerable AE, a life-threatening bleeding episode, eg, any gastrointestinal hemorrhage or intracranial hemorrhage, or life-threatening thromboembolic event
- Requires a prohibited medication
- More than 1 AT measurement <15% if at a dose of 50 mg Q2M

The Investigator will confer with the Sponsor or study Medical Monitor before discontinuing dosing in the patient.

Patients (or their guardians) may decide to discontinue study drug.

In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments through the end of study so that their experiences are captured in the final analyses. If a patient discontinues dosing due to a serious adverse event (SAE), the SAE should be followed as described in Section 7.6.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the appropriate section of the eCRF. Patients who discontinue study drug but who remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable. Safety will be captured for the entire duration of study for patients who discontinue treatment.

### 5.3.2 Withdrawal from study

A patient or guardian may withdraw consent from study participation at any time. The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest. Any withdrawal from the study must be fully documented in the eCRF and should be followed-up by the Investigator.

However, study integrity and interpretation is best maintained if all enrolled patients continue study assessments and follow-up even if study treatment is discontinued. Patients considering withdrawing from the study should be informed that they can discontinue treatment and still remain in the study to complete study assessments and follow-up as specified in the Schedule of Assessments (Table 1). If a patient still chooses to discontinue study treatment and withdraw from all follow-up, every effort should be made to conduct the EOS/ET assessments within 4 weeks of the last dose (see Table 1). When a patient withdraws from the study, the withdrawal of consent and the reason for withdrawal must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. There will be no replacements of patients who withdraw from this study.

### 5.3.3 Criteria for temporarily delaying enrollment or administrations of study intervention

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Section 11.8 for screening, enrollment and/or administration of study intervention.

# 6 TREATMENTS

## 6.1 TREATMENTS ADMINISTERED

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

The IMP may be supplied at the site or from the Investigator/site/Sponsor to the patient via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the patient.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 11.8.

## 6.2 INVESTIGATIONAL MEDICINAL PRODUCT

Detailed information describing the preparation, administration, and storage of fitusiran is provided in the Pharmacy Manual.

### 6.2.1 Description

Fitusiran (SAR439774) solution for injection (SC use) will be supplied as a sterile solution (see Pharmacy Manual for further details of solution concentration and fill volume).

### 6.2.2 Dose and administration

Patients will receive open-label fitusiran as an SC injection, during the fitusiran treatment period for a total of 7 months; dosing will begin on Day 1 of the fitusiran treatment period (Table 1).

Study drug injection will be administered at the clinic by qualified staff under the supervision of the Investigator or designee. Detailed instructions for study drug administration are found in the Pharmacy Manual.

Study drug will not be blinded as this is an open-label study. See Section 6.2.5 regarding packaging and labeling.

If a patient does not receive a fitusiran dose within the specified dosing window (Table 1), the Investigator should contact the study Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

If a patient misses a dose, the Investigator, in consultation with the study Medical Monitor, will discuss whether the patient will be able to continue on the study.

Additional details regarding dosing can be found in the Pharmacy Manual.

### 6.2.3 Dose modifications

Instructions for AT-driven fitusiran regimen modification are provided in Section 6.2.3.2. If an IMP-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the fitusiran dose may be held at the discretion of the Investigator and the study Medical Monitor should be contacted.

#### *6.2.3.1 LFT criteria for withholding, monitoring, and stopping fitusiran dosing*

1. LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose of fitusiran. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3× ULN central laboratory results should be used to guide subsequent monitoring as detailed in Table 4.
3. For any ALT or AST elevation >3× ULN:
   a) Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b) Perform assessments per Table 4 and Table 7.
   c) If an alternative cause is found, provide appropriate care.
4. For any ALT or AST elevation >3× ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2× ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3× ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2× ULN or INR ≥1.5, see Table 4 below:

**Table 4 - Monitoring and dosing rules for asymptomatic patients with confirmed isolated elevations of ALT and/or AST >3× ULN, with no alternative cause identified**

| Transaminase Level | Action |
|---|---|
| >3× to 5× ULN | • May continue dosing<br>• Evaluate the initial elevation in LFT per the following assessments:<br>- Table 8 (all assessments to be performed once)<br>- Hematology, serum chemistry, LFT, and coagulation per Table 7<br>- AT<br>• Monitor at least every two weeks (hematology, serum chemistry, LFT, and coagulation per Table 7 and AT)<br>• If elevation persists for ≥2 months, must discuss with the study Medical Monitor before continuing dosing |

**Table 4 - Monitoring and dosing rules for asymptomatic patients with confirmed isolated elevations of ALT and/or AST >3× ULN, with no alternative cause identified**

| Transaminase Level | Action |
|---|---|
| >5× to 8× ULN | • Hold fitusiran dose until recovery to ≤1.5× ULN; may resume dosing after discussion with the study Medical Monitor<br>• Evaluate the initial elevation in LFT per the following assessments:<br>- Table 8 (all assessments to be performed once)<br>- Hematology, serum chemistry, LFT, and coagulation per Table 7<br>- AT<br>• Monitor at least weekly (hematology, serum chemistry, LFT, and coagulation per Table 7 and AT) until ALT and/or AST is declining on two consecutive draws, then may decrease monitoring to biweekly<br>• If ALT or AST rises to >5× ULN following repeat dosing, permanently discontinue dosing |
| >8× ULN | • Permanently discontinue dosing after confirmation of the transaminase value |

Note: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

#### *6.2.3.2 Antithrombin level criteria for a dose adjustment*

With amendment 6, patients will resume dosing at a dose of 50 mg Q2M (Table 1). Patients rolling over from this study to the extension study may have the option for dose escalation in that study if dose escalation criteria defined in that protocol are met.

Upon the first AT level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the result. If this result is <15%, this will be considered the second AT activity level <15%. Patients receiving fitusiran at a dose of 50 mg Q2M with more than 1 AT activity level <15% at any time during the study must permanently discontinue fitusiran.

See the rationale for a new dosing justification in Section 1.4.

#### *6.2.3.3 Temporary discontinuation due to a regional or national emergency*

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 11.8). For all temporary intervention discontinuations, the associated reason/emergency should be recorded by the Investigator (or designee) in the appropriate pages of the eCRF.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 11.8.

### 6.2.4 Preparation, handling, and storage

Qualified staff at each clinical study center will be responsible for preparation of fitusiran doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored per the Pharmacy Manual and refrigerated at approximately 5±3°C. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage details are provided in the Pharmacy Manual.

### 6.2.5 Packaging and labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practices, or local applicable regulations, where necessary. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

### 6.2.6 Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drug.

Further instructions about drug accountability are detailed in the Pharmacy Manual.

Any quality issue noticed with the receipt or use of an investigational medicinal product (IMP) (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 7.6.6.8).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for Direct-to-Patient [DTP] shipment, for which a courier company has been approved by the Sponsor), allow

the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

## 6.3 CONCOMITANT MEDICATIONS

Use of concomitant medications will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Local standard treatment of hemophilia is considered to be, but not limited to, intravenously (IV) infusion of FVIII or FIX concentrates, aPCC, or rFVIIa. Use of these agents will be captured in the patient's eDiary.

Use of prothrombin complex concentrates for bleeding episode management is not permitted.

Antifibrinolytics may be used as single agents but may not be used in combination with factor or BPA. Use of aPCC and rFVIIa as combination therapy is not recommended.

### 6.3.1 Factor concentrates or bypassing agent prophylaxis

#### *6.3.1.1 Routine use of factor or bypassing agent prophylaxis in the factor or bypassing agent prophylaxis period*

During the factor or BPA prophylaxis period, patients will continue to receive prophylaxis with their usual products on a regimen consistent with recommendations in the approved prescribing information, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding. The regimen used during the factor or BPA prophylaxis period must have a minimum frequency of administration as presented in Table 5. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. For the United States specific requirements, see Section 11.6.1.2.

**Table 5 - Factor or bypassing agent prophylaxis requirements**

| Type of Factor or BPA replacement | Frequency of administration |
|---|---|
| Standard half-life FVIII | Twice weekly |
| Extended half-life FVIII | Once weekly |
| Standard half-life FIX | Once weekly |
| Extended half-life FIX | Once biweekly |
| aPCC | Twice weekly |
| rFVIIa | Every other day |

Abbreviation: aPCC= activated prothrombin complex concentrates; BPA=bypassing agent; FVIII = Factor VIII; FIX = Factor IX; rFVIIa=recombinant Factor VIIa Note: For the United States specific requirements, see Section 11.6.1.2.

#### *6.3.1.2 Management of factor or bypassing agent prophylaxis during the transition to the fitusiran treatment period*

The first 28 days of fitusiran treatment is referred to as the onset period. During the onset period AT lowering will be progressing toward therapeutic levels. Patients will continue factor or BPA prophylaxis with minimum frequency as in Table 5, for the first 7 days of the fitusiran onset period. Subsequent to Day 7 of the fitusiran treatment period, factor concentrates or BPAs should be administered only for bleeding episodes or if needed in advance of invasive medical procedures. For the United States specific requirements, see Section 11.6.1.2.

### 6.3.2 Management of bleeding episodes

The occurrence of bleeding episodes is a typical characteristic of hemophilia (3, 13, 14); bleeding episodes will be recorded as efficacy assessments of fitusiran and will not be considered as AEs unless the criteria for SAEs are met (see adverse events definitions in Section 7.6.6.1). Bleeding episodes will be recorded in the eDiary. For bleeding episodes in which there was no factor or BPA infusion or other type of intervention employed, the reason the bleeding episodes were untreated will be recorded in the eDiary (see Section 7.2.1).

Investigators will establish and provide instructions for an individualized bleed management plan based on the guidelines in Table 6 for each patient.

The bleed management plan should be reviewed by the Investigator or designee with the patient at each clinic visit (and contact every 2 weeks between clinic visits) and updated as necessary.

For the United States specific requirements, see Section 11.6.1.2.

#### *6.3.2.1 Bleeding episode management recommendations for patients during the factor or bypassing agent prophylaxis period (patients not receiving fitusiran)*

During the factor or BPA prophylaxis period, bleeding management therapy with factors or BPAs will be managed based on the local standard practice for treating hemophilia patients, as routinely administered by the physician. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. Where clinical circumstances allow, it is recommended that the patient contact the Investigator for all events that may be suspected to be or are characteristic of a bleeding episode. If adequate hemostasis does not occur after two doses of factor or BPA, the patient should contact the site for further instruction. If the patient feels the need to administer doses higher than the patient's bleeding episode management plan recommends, or at a higher frequency, it is recommended that the patient contact the site. See Section 7.2.1 regarding patient use of the eDiary and site alerts that will assist in this process. For the United States specific requirements, see Section 11.6.1.2.

#### *6.3.2.2 Bleeding episode management recommendations for patients during the fitusiran treatment period (for the United States specific requirements, see Appendix 11.5.1.2)*

Given the mechanism of action and pharmacodynamics profile of fitusiran, the factor or BPA dose necessary to safely and effectively treat breakthrough bleeding episodes in patients receiving fitusiran during the fitusiran treatment period will be lower than standardly prescribed. This is supported by data from the Phase 1 study in which bleed events were managed with factor or BPA, as well as additional modeling and ex vivo spiking data. More detailed information on the clinical experience in bleeding episode management in Phase 1 and Phase 1/2 fitusiran studies, as well as supportive nonclinical studies is provided in the Investigator's Brochure.

After administration of fitusiran, AT lowering will be progressing toward therapeutic levels. As quickly as 7 days after the initial fitusiran dose, the majority of patients will have AT levels at or below 60% residual activity. By 14 days after dosing, it is expected that 94% of patients will have AT lowering of >50%, with a median value of 66.8%. Based on these AT kinetics, it is recommended that patients continue with their standard factor or BPA regimens for the first 7 days following initiation of fitusiran dosing, with institution of the protocol-specific bleed management guidelines with reduced factor or BPA at Day 8 and beyond (Table 6).

Patients on fitusiran will be provided a written bleed management plan with appropriate dosing of factor or BPA for use during Day 1 through 7, as well as a bleed management plan with dosing for Day 8 and beyond. Thereafter the bleed management plan will be reviewed and updated at monthly visits, and new written plans provided to the patient if dosing changes.

Importantly, after Day 7 of the fitusiran treatment period, patients should not use factor, BPA, or other hemostatic agents as prophylaxis for bleeding episode prevention, including doses related to anticipated hemostatic challenges such as physical activity. For prophylaxis of bleeding episodes in patients who require operative procedures see Section 6.6.

**Bleed Management Guidelines Day 1 to Day 7 of Fitusiran Treatment Period:**

Patients should be instructed to call the site prior to administering factor or BPA for the management of bleeding episodes. Patients should continue with their standard factor or BPA regimens.

**Bleed Management Guidelines Day 8 and Beyond of Fitusiran Treatment Period:**

When a patient experiences symptom that may be consistent with bleeding episodes, the following steps should be followed:

1. Patient should be instructed to call the study center to discuss symptoms to determine whether or not they are consistent with a bleeding event and to discuss the appropriate factor and/or BPA dose to use. This interaction between patient and Investigator is recommended prior to the administration of each dose of factor or BPA. Confirmation of bleeds at the study center prior to treatment may be considered. Such visits should capture assessments per Section 6.4 and Table 2.

2. If a determination is made that symptoms require treatment, the recommended treatment algorithm for bleeding episodes is described below:

1. A single dose can be administered according to the guidelines in Table 6.
2. The patient should be instructed to re-evaluate symptoms in 24 hours for bleeds treated with FVIII, FIX or aPCC and in 2-3 hours for bleeds treated with rFVIIa.
   a) Administration of FIX Extended half-life should not be more frequent than every 5-7 days.
3. If a second dose (in the case of FVIII, FIX or aPCC) or a third dose (in the case of rFVIIa) is needed, the patient must call the study center before dosing.
   a) Consider evaluation and treatment of the patient at the study center and confirmation of bleeds when any repeated doses are needed (See Section 6.4 and Table 2).
   b) If more than two doses of FVIII, FIX or aPCC or three doses of rFVIIa are needed, the patient should be seen at the study center within 48-72 hours.
4. Doses should not be administered at less than 24-hour intervals (except rFVIIa as indicated in Table 6).
5. Doses should not exceed the protocol maximum recommended dose indicated in Table 6.
6. Consultation with the study Medical Monitor and Clinical Advisor should be considered for clinical circumstances below, that may warrant AT replacement:
   a) Doses of factor or BPA higher than those recommended in Table 6
   b) Dosing of factor or BPA at decreased intervals than those recommended in Table 6
   c) Multiple or repeated doses of factor or BPA
7. Antifibrinolytics may not be used in combination with factor or BPA.

**Table 6 - Bleed management dosing guidelines by specific product**

| | Factor VIII | Factor IX Standard half-life | Factor IX Extended half-life | aPCC | Recombinant Factor VIIa |
|---|---|---|---|---|---|
| **Recommended single dose of** | 10 IU/kg | 20 IU/kg | 20 IU/kg | 30 U/kg | ≤45 µg/kg |
| **Single Dose should not exceed** | 20 IU/kg | 30 IU/kg | 30 IU/kg | 50 U/kg | 45 µg/kg |
| **Repeat dose instructions** | Mandatory to call the clinical study center prior to second dose<br>Consider evaluation and treatment at the clinical study center (see Section 6.4) | | | | Mandatory to call site prior to third dose |

| | | | | | |
|---|---|---|---|---|---|
| | Should not repeat in less than 24 hours | Should not repeat in less than 24 hours | Should not repeat in less than 5-7 days | Should not repeat in less than 24 hours | Should not repeat in less than 2 hours |
| | Should be seen at site within 48-72 hours if more than 2 doses are required (see Schedule of Assessments Table 1 for assessments) | | | | Should be seen at site within 48-72 hours if more than 3 doses are required |
| | **For situations requiring higher doses, more frequent administration, multiple repeated doses, discussion with study Medical Monitor and Clinical Advisor is recommended, and AT replacement should be considered.** Do not use antifibrinolytics in combination with factor or BPA. | | | | |

Note: Adjunctive management of bleeding episodes should be carried out per standard of care. For the United States specific requirements, see Section 11.6.1.2. For the Japan specific requirements, see Section 11.6.2.

#### *6.3.2.3 Use of factor or bypassing agents following discontinuation of fitusiran (for the United States specific requirements, see Appendix 11.5.1.2)*

**Resuming routine prophylaxis following discontinuation of fitusiran**

Patients who opt to discontinue fitusiran may resume standard prophylaxis with factor concentrates or BPAs when their AT activity level returns to approximately 60% (per the central laboratory). An earlier restart of standard treatment may be considered in conjunction with consultation from the study Medical Monitor, if a strong medical need arises (eg, increased frequency of bleeding).

**Bleed episode management following discontinuation of fitusiran**

Patients who opt to discontinue fitusiran may resume standard on-demand dosing with factor concentrates or BPAs for bleeding episodes when their AT residual activity level returns to approximately 60% (per the central laboratory). An earlier restart of standard treatment may be considered in conjunction with consultation from the study Medical Monitor, if a strong medical need arises (eg, increased frequency of bleeding). If full doses of factor or BPA are required to achieve hemostasis prior to AT recovery (approximately 60% residual activity per the central laboratory), AT replacement should be considered.

### 6.3.3 Other concomitant medications

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must be able to tolerate them and have had no previous side effects (eg, gastric distress or bleeding).

Use of >4 g acetaminophen per day is not permitted.

Treatment for HIV is permitted and must be recorded as concomitant medication.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

Any concomitant medication that is required for the patient's welfare may be prescribed by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

## 6.4 ASSESSMENT OF COAGULATION PARAMETERS AT THE TIME OF A BLEED

Any patient who presents to the clinical study center for evaluation of symptoms that are suspected as characteristic of a bleeding episode, the patient should be assessed by the Investigator to determine whether symptom(s) require treatment. If treatment is required, blood samples should be collected predose and postdose and assessments performed as scheduled in Table 2.

If a patient presents following administration of factor or BPAs at home and within 48 hours of the dose, and no further treatment is given at the center, AT and the postdose assessments in Table 2 should be obtained in a single draw at any time during the visit.

## 6.5 MONITORING AND MANAGEMENT OF THROMBOTIC EVENTS

As serious vascular (arterial and venous) thrombotic events have been reported in patients exposed to fitusiran, Investigators should have a low threshold to evaluate signs and symptoms potentially consistent with these diagnoses. Signs and symptoms of vascular thrombotic events may include, but are not limited to, severe or persistent headache, headache with nausea and vomiting, chest pain and/or tightness, coughing up blood, trouble breathing, abdominal pain, fainting or loss of consciousness, swelling or pain in the arms or legs, vision problems, weakness and/or sensory deficits, and changes in speech.

An evaluation of signs and symptoms potentially consistent with vascular thrombosis should include appropriate imaging studies as applicable. For the diagnosis of cerebral venous sinus thrombosis magnetic resonance imaging venogram (MRV) or computed tomography venogram (CTV) is recommended (15).

If a patient develops thrombosis while on fitusiran, AT reversal is recommended in combination with factor or BPA replacement and appropriate anticoagulation. AT reversal should follow labeled product recommendations for the prevention of perioperative thrombosis in patients with AT deficiency, and individualize patient doses to target 80-120% AT activity. The use of plasma derived AT may be preferable to recombinant AT, given its longer half-life. It is recommended that cases of thrombosis are discussed with the study Medical Monitor and Clinical Advisor (see Section 7.6.6.1 for further information regarding Adverse Events of Special Interest). For the United States specific requirements, see Section 11.6.1.2. For the Japan specific requirements, see Section 11.6.2.

## 6.6 ELECTIVE AND/OR EMERGENCY SURGERY

If an urgent need for major surgery arises during the study period, the study Medical Monitor will be informed and a written perioperative treatment plan will be reviewed with the study Medical Monitor before conducting the procedure, 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 undergoing major surgery during the study, 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 6.3.2 and the guideline below:

- If the clinical circumstance is such that the recommended doses and/or dose intervals in Table 6 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 Section 11.2.1, and as scheduled in Table 12.

## 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 bleeding (16, 17). 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 per local regulations. For the Japan specific requirements, see Section 11.6.2.

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 ~13-months, except for patients in the subgroup of Cohort A, which is up to 7 months, of eDiary recording (including both the 6-month factor or BPA prophylaxis period [6-month BPA prophylaxis period is not applicable for the subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment] and 7-month fitusiran treatment period). For the United States specific requirements, see Section 11.6.1.2.

## 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.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 11.8.

## 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 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 factor concentrate and/or BPA prescriptions (in the medical or pharmacy record) and documentation of reported number of bleeding episodes over the last 6 months (for inhibitor patients) or 12 months (for non-inhibitor patients). 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 study 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).

For the United States specific requirements, see Section 11.6.1.2.

### 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 or BPA infusion, eg, hemarthrosis, muscle, or mucosal bleeding episodes. 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 7.6.6.1.

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 (18).

The start time of a bleeding episode will be considered the time at which symptoms of 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 6.3.2.

For the United States specific requirements, see Section 11.6.1.2.

### 7.2.1 Electronic diary

Patients will be issued an eDiary to record all bleeding events and all doses of factors or 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 factors or BPAs, and reasons for dosing (prophylaxis, treatment of a bleeding episode, and preventive dose for anticipated activity). Training of patients should be documented in the appropriate source record.

The Sponsor will review diary entries for data quality to identify issues such as patients who may need retraining on eDiary 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) continuously for the study duration. The site will contact the patient at a minimum interval of every 2 weeks (+/- 4 days) per schedule of assessments to review eDiary 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 bleed. 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 factor or 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.

For the United States specific requirements, see Section 11.6.1.2.

## 7.3 PHARMACODYNAMIC ASSESSMENTS

In this study AT activity level and thrombin generation will be collected as measurements of PD effect and coagulation assessments are collected for exploratory analyses 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). On dosing days, 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.

Following final fitusiran dose, and in case the patient is not rolled over to the open label 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.

### 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 Coagulation/Thrombin generation response assessment in factor or bypassing agent prophylaxis period

During the factor or BPA prophylaxis period (before fitusiran treatment), patients will undergo a coagulation and peak thrombin/thrombin generation response assessment with timed blood collections both before and following a dose of their routine factor or BPA prophylaxis doses. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. For these patients, the coagulation and peak thrombin/thrombin generation response assessment are not applicable. For the United States specific requirements, see Section 11.6.1.2.

These laboratory assessments are collected for research purposes, will be run centrally, and will not be released to sites or used to guide study conduct or clinical management.

### 7.3.4 Exploratory analyses

Except where prohibited by local or national regulations, in consented patients (since optional), 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 (since optional), serum samples may be used for analysis of circulating RNA, including the assessment of cleaved antithrombin 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 according to the collection schedule presented in Table 11, 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 11) will be summarized and analyzed using a population PK approach and noncompartmental analysis, as applicable.

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 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict patient response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by patients (see Section 9.1.1) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For patients who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study patients will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to patients in the ICF.

All study patient data and samples will be coded such that no patient direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting patient confidentiality and personal data (see Section 11.5).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a patient requests destruction of their samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

Study patient coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study patient who has requested the destruction of his/her samples).

Patient's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

## 7.6 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.

### 7.6.1 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.

### 7.6.2 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.

### 7.6.3 Physical examination

Full and directed physical examinations will be conducted according to 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 12).

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

### 7.6.4 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 at sites.

### 7.6.5 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 study drug 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 7 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 7 which are performed at the clinic should also be repeated at 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 7 - 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 | 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 |

**Table 7 - Clinical laboratory assessments**

| | |
|---|---|
| Ketones | Urobilinogen |
| Glucose | Leukocytes |
| Protein | Microscopy (if clinically indicated) |
| **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>HBc antibody, IgM and IgG | Hepatitis E, including:<br>HEV antibody IgM and IgG |
| **Immunogenicity** | |
| Antidrug Antibodies | |

Note: All assessments will be measured in the central laboratory

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FIX=Factor IX; FVIII=Factor VIII; GGT= gamma glutamyl transferase; HAV=hepatitis A virus; HBsAg=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.

#### *7.6.5.1 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 during either the factor or BPA prophylaxis period (BPA prophylaxis period is not applicable for the subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment) or the fitusiran treatment period. Following the occurrence of elevated liver transaminases or other LFT abnormalities per the central laboratory, all assessments in Table 8 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 7, AT levels, and other assessments or evaluations per Investigator discretion, as appropriate. For the United States specific requirements, see Section 11.6.1.2.

For patients in the fitusiran treatment period, monitoring and dose modification will also be performed as outlined in Section 6.2.3.1.

**Table 8 - 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 2[a] | 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; HBsAg=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.

#### *7.6.5.2 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 study drug 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.

### 7.6.6 Adverse events

#### *7.6.6.1 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 adverse event (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 7.6.6.1.

**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 as an 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.
- Cholecystitis
- Cholelithiasis

**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 adverse event |

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. |

#### *7.6.6.2 Eliciting and recording adverse events*

**Eliciting Adverse Events**

The patient should be asked about medically relevant changes in his health since the last visit, with attention to any signs and symptoms that could be consistent with thrombosis. The patient should also be asked if he has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over the counter [OTC]). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

**Recording Adverse Events**

The Investigator is responsible for recording non-serious AEs and SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to investigational drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AESI (Section 7.6.6.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AESI eCRF. Additional clinical and laboratory information may be collected; see Section 6.2.3.1 regarding monitoring for liver abnormalities.

Refer to the eCRF completion guidelines for details on reporting events in the supplemental AESI eCRF.

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 7.6.6.1. The manifestation and frequency of bleeding episodes is an efficacy indicator of this study and ABR is the focus of the primary and secondary efficacy analyses.

**Recording an ISR**

For all ISRs, the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, event outcome). An ISR is defined as a local reaction at or near the site of injection. “At or near” the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur

with swelling or hematoma). Reactions with onset and resolution within 4 hours of the injection eg, transient pain/burning at injection site) do not meet the study definition of ISRs, unless immediate treatment is required. A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

#### *7.6.6.3 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 7.6.6.1 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 study drug.

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 study drug, 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.

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 study drug, 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.

#### *7.6.6.4 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.

#### *7.6.6.5 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.

#### *7.6.6.6 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.

#### *7.6.6.7 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.

#### *7.6.6.8 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.

## 7.7 OTHER ASSESSMENTS

### 7.7.1 Patient-reported outcomes

Patient-reported outcomes will be utilized in this study where available to assess health-related quality of life (HRQOL), physical activity, and treatment satisfaction and health utility. The age of the patient at Enrollment will determine which age-specific versions of 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 at study sites.

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

#### *7.7.1.1 HRQOL instruments: Haem-A-QOL and Haemo-QOL*

The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) and Haemophilia Quality of Life Questionnaire for Children and Adolescents (Haemo-QOL) are psychometrically tested QOL assessment instruments for patients with hemophilia (19). 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 Month 7 visit will be utilized throughout the study.

#### *7.7.1.2 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 (20). Where available, the TSQM questionnaire will be distributed to patients to self-complete as specified in the Schedule of Assessments (Table 1).

#### *7.7.1.3 HAL*

The Haemophilia Activities List (HAL) and Paediatric HAL (pedHAL) questionnaires will assess subjective functional ability to perform activities of daily living (21). 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 and pedHAL questionnaire will be distributed to patients to self-complete as specified in the Schedule of Assessments (Table 1).

#### *7.7.1.4 EQ-5D-5L*

The EQ-5D-5L is a standardized instrument for use as a measure of QOL outcome (22). 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 all patients as specified in the Schedule of Assessments (Table 1).

### 7.7.2 HJHS

The HJHS is a tool for assessment of joint health in subjects with hemophilia (23). 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 at study sites.

# 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.

The primary efficacy and safety analyses will be done for Cohort A and Cohort B separately. A pooled analysis will be performed after all patients have either finished the Month 7 visit during the fitusiran treatment period or discontinued from the study.

## 8.1 DETERMINATION OF SAMPLE SIZE

Sample size is based on clinical considerations. The overall sample size of 80 patients including approximately 30 patients with inhibitor (Cohort A) and approximately 50 patients without inhibitor (Cohort B) was selected recognizing the limited number of patients with hemophilia, and to yield a reasonably robust estimate of the fitusiran bleeding episode rate and address the secondary objectives, including characterization of safety and tolerability. The proposed sample size is also expected to provide reasonable precision around the ratio of bleeding rate in the fitusiran efficacy period to bleeding rate in the factor or BPA prophylaxis period for both Cohort A and Cohort B.

Since patients will participate in multiple periods, within-patient correlation of numbers of bleeding episodes is expected between the periods. Having no prior knowledge of this correlation, different correlation scenarios were considered and the ratio of the bleeding rate in fitusiran efficacy period to the bleeding rate in factor or BPA prophylaxis period along with its 95% CIs were simulated. For the United States specific requirements see Section 11.6.1.2.

Table 9 and Table 10 summarizes the results from 10,000 simulated studies along with the ABR assumptions.

**Table 9 - Simulated ratio of rates for Cohort A, with 95% confidence intervals**

| Correlation | Average Ratio (Average 95% CI Bounds), N=30 Based on 10,000 Simulations | |
|---|---|---|
| | Fitusiran period ABR: mean=4, SD=6 | |
| | Factor/BPA period ABR: Mean=16; SD=14 | Factor/BPA period ABR: Mean=12; SD=11 |
| 0.25 | 0.24 (0.14, 0.42) | 0.32 (0.19, 0.57) |
| 0.50 | 0.24 (0.15, 0.39) | 0.32 (0.20, 0.52) |
| 0.75 | 0.24 (0.17, 0.35) | 0.32 (0.22, 0.47) |

Abbreviation: ABR=annualized bleeding rate; BPA=bypassing agent; CI=confidence interval; SD=standard deviation

Note: Correlation = within-patient correlation between bleeding episodes of fitusiran efficacy period and factor or BPA period. BPA period ABR per Oldenburg, et al (24).

**Table 10 - Simulated ratio of rates for Cohort B, with 95% confidence intervals**

| Correlation | Average Ratio (Average 95% CI Bounds), N=40 Based on 10,000 Simulations | |
|---|---|---|
| | Fitusiran period ABR: mean=4, SD=6; N=40 | |
| | Factor/BPA period ABR: Mean=4; SD=5 | Factor/BPA period ABR: Mean=6; SD=7 |
| 0.25 | 1.04 (0.57, 1.94) | 0.69 (0.39, 1.25) |
| 0.50 | 1.03 (0.63, 1.69) | 0.68 (0.43, 1.09) |
| 0.75 | 1.01 (0.72, 1.41) | 0.67 (0.48, 0.93) |

Abbreviation: ABR=annualized bleeding rate; BPA=bypassing agent; CI=confidence interval; SD=standard deviation
Note: Correlation = within-patient correlation between bleeding episodes of fitusiran efficacy period and factor or BPA period. BPA period ABR per Oldenburg, et al (24).

## 8.2 STATISTICAL METHODOLOGY

The statistical and analytical plans presented below are brief summaries of planned analyses. The analyses will be done for Cohort A, and Cohort B separately. A pooled analysis will be performed after all patients in the 2 cohorts have either finished the Month 7 visit during the fitusiran treatment period or discontinued from the study. More complete plans will be described in the SAP. 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:

- **Safety Analysis Set:** All patients who enrolled and then received any dose of fitusiran.
- **Efficacy Analysis Set (EAS):** All patients in the safety analysis set who received both factor or BPA prophylaxis and any dose of fitusiran (Addressed in more detail in SAP).
- **Per-protocol Analysis Set (PPS):** All patients in the EAS who had no major protocol deviations. Major deviations will be specified in the SAP.
- **PK Analysis Set:** All patients who received any dose of study fitusiran and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- **COVID-19 Unaffected Set**: All patients who had no major or critical protocol deviations due to COVID-19 at any visit up to the end of study (Month 7).
- The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will be included in the safety analysis set but will not be part of the efficacy analysis set; however, their efficacy data will be presented separately.

### 8.2.2 Examination of subgroups

Exploratory subgroup analysis on ABR will be conducted for the primary endpoint. 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.

### 8.2.4 Baseline evaluations

Demographics and other baseline characteristics will be summarized for the Safety Analysis Set and EAS.

### 8.2.5 Efficacy analyses

Primary analyses of the primary and secondary endpoints will be based on the EAS.

To address the potential impact of COVID-19, the efficacy analyses will be repeated on the COVID-19 unaffected set. Additional analyses and methods required to evaluate the impact are detailed in the SAP.

#### *8.2.5.1 Primary endpoint*

The primary analysis will be performed on the EAS and will include all bleeding episodes occurring in the factor or BPA prophylaxis period (Day -162 to Day -1) and the fitusiran efficacy period (Day 29 to Day 190). If a patient does not have bleeding episode data collected after Day 28 (eg, due to early study discontinuation), the available bleeding episode data starting from Day 1 will be used in the primary analysis. To avoid confounding the treatment effect, bleeding episode data during and after major surgery, antithrombin administration, major trauma, or initiation of prophylaxis treatment with factors or BPAs during the fitusiran treatment period will be excluded from the primary analysis.

The number of bleeding episodes will be analyzed using a repeated measures negative binomial model with fixed effect of treatment period. The logarithm number of days that each patient spends in the efficacy period matching the bleeding episode data being analyzed will be included as an offset variable to account for unequal follow-up time due to early withdrawal or surgery. The ratio of bleeding rates in the fitusiran efficacy period to the factor or BPA prophylaxis period and its 95% CI and p-value will be presented. The p-value should be interpreted with caution. In addition, as a contrast Bayesian analyses will be performed to summarize the point estimates of the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty. The estimated mean ABRs in these 2 periods along with their 95% CIs will be presented from this model. In addition, summary statistics for ABR, including the median and interquartile range, will be presented for each treatment arm, where ABR is defined as:

$$\frac{\text{total number of qualifying bleeding episodes}}{\text{total number of days in the respective period}} \times 365.25$$

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

For the United States specific requirements, see Section 11.6.1.2.

#### *8.2.5.2 Secondary endpoints*

Spontaneous bleeding episodes and joint bleeding episodes will be analyzed using the same method as primary analysis of ABR. Summary statistics, including the median and interquartile range, for annualized spontaneous bleeding rate and annualized joint bleeding rate will be reported.

Change in Haem-A-QOL physical health score and total score (in patients ≥17 years of age) in the factor or BPA prophylaxis period and fitusiran treatment period will be summarized descriptively. A mixed model for repeated measures analysis may be performed as deemed appropriate.

The bleeding episodes in the fitusiran onset period and in the fitusiran treatment period will be analyzed using a negative binomial model with logarithm of follow-up time in the period as an offset parameter. Summary statistics, including the median and interquartile range, for the ABR in 2 periods will be reported.

The secondary endpoint of annualized weight-adjusted consumption of factor/BPA injections will be summarized using descriptive statistics

#### *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 all patients. The details of analysis will be presented in a separated 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 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 results will be based on all AEs having onset (start or worsening in severity) within the analysis period 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 provided 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 analyses

Antidrug antibody results will be summarized descriptively.

### 8.2.10 Interim analysis

An interim analysis may be conducted as a part of this study.

# 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 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.

### 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:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study intervention development

## 9.2 DATA QUALITY CONTROL AND QUALITY ASSURANCE

### 9.2.1 Data handling

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All patient data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

### 9.2.2 Study monitoring

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 9.2.3 Audits and inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor, or its designee, immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

## 9.3 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 9.4 DISSEMINATION OF CLINICAL STUDY DATA

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include www.clinicaltrials.gov, www.clinicaltrialregister.eu, and www.sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to www.clinicalstudydatarequest.com.

Individual patient data and supporting clinical documents are available for request at www.clinicalstudydatarequest.com. While making information available we continue to protect the privacy of patients in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: www.clinicalstudydatarequest.com.

# 10 LIST OF REFERENCES

1. Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, Germini F; Data and Demographics Committee of the World Federation of Hemophilia. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019 Oct 15;171(8):540-46.

2. What is hemophilia? Word Federation of Hemophilia [Internet]. 2004 [cited 2020 Aug 17]. Available from: http://www1.wfh.org/publications/files/pdf-1324.pdf.

3. Bauer KA. Current challenges in the management of hemophilia. Am J Manag Care. 2015;21(6 Suppl):S112-22.

4. Sehgal A, Barros S, Ivanciu L, Cooley B, Qin J, Racie T, et al. An RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis in hemophilia. Nat Med. 2015;21(5):492-7.

5. Walsh CE, Soucie JM, Miller CH. Impact of inhibitors on hemophilia A mortality in the United States. Am J Hematol. 2015;90(5):400-5.

6. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia. 2003 Jul;9(4):418-35.

7. Peyvandi F, Ettingshausen CE, Goudemand J, Jiménez-Yuste V, Santagostino E, Makris M. New findings on inhibitor development: from registries to clinical studies. Haemophilia. 2017 Jan;23 Suppl 1:4-13.

8. Puetz J, Soucie JM, Kempton CL, Monahan PE; Hemophilia Treatment Center Network (HTCN) Investigators. Prevalent inhibitors in haemophilia B subjects enrolled in the Universal Data Collection database. Haemophilia. 2014 Jan;20(1):25-31.

9. Brettler DB. Inhibitors in congenital haemophilia. Baillieres Clin Haematol. 1996 Jun;9(2):319-29.

10. Pasi KJ, Rangarajan S, Georgiev P, Mant T, Creagh MD, Lissitchkov T, et al. Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy. N Engl J Med. 2017 Aug 31;377(9):819-28.

11. Machin N, Ragni MV. An investigational RNAi therapeutic targeting antithrombin for the treatment of hemophilia A and B. J Blood Med. 2018 Aug 22;9:135-140.

12. Schrijvers L, Beijlevelt-Van der Zande M, Peters M, Lock J, Cnossen M, Schuurmans M, et al. Achieving self-management of prophylactic treatment in adolescents: The case of haemophilia. Patient Educ Couns. 2016.

13. Makris M, Kasper C. The World Federation of Hemophilia guideline on management of haemophilia. Haemophilia. 2013;19(1):1.

14. Witkop M, Guelcher C, Forsyth A, Hawk S, Curtis R, Kelley L, et al. Treatment outcomes, quality of life, and impact of hemophilia on young adults (aged 18-30 years) with hemophilia. Am J Hematol. 2015;90 Suppl 2:S3-10.

15. Saposnik G, Barinagarrementeria F, Brown RD, Jr., Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-92.

16. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.

17. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol. 2009;145(1):24-33.

18. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. 2014;12(11):1935-9.

19. Wyrwich KW, Krishnan S, Poon JL, Auguste P, von Maltzahn R, Yu R, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Haemophilia. 2015;21(5):578-84.

20. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.

21. van Genderen FR, Westers P, Heijnen L, de Kleijn P, van den Berg HM, Helders PJ, et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. Haemophilia. 2006;12(1):36-46.

22. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

23. Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, van der Net J, et al. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. Arthritis Care Res (Hoboken). 2011;63(2):223-30.

24. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. 2017;377(9):809-18.

# 11 APPENDICES

## 11.1 PHARMACOKINETIC ASSESSMENT TIME POINTS

Table 11 provides a schedule for the collection of blood samples for PK analysis in East Asian patients).

**Table 11 - Pharmacokinetic time points in East Asian patients at East Asian sites following fitusiran administration at 50 mg Q2M**

| Study day | Protocol time (hh:mm) | PK blood |
|---|---|---|
| Day 1 | Predose (within 240 minutes before dosing) [a] | X |
| | 00:30 (±5 min) [a] | X |
| | 01:00 (±5 min) [a] | X |
| | 02:00 (±15 min) [a] | X |
| | 04:00 (±30 min) [a] | X |
| | 06:00 (±30 min) [a] | X |
| | 08:00 (±30 min) [a] | X |
| | 12:00 (±30 min) [a] | X |
| Month 2 | Predose (within 240 minutes before dosing) [a] | X |
| Month 4 | Predose (within 240 minutes before dosing) [a] | X |
| | 04:00 (±30 min) [a] | X |
| Month 6 (EOT) | Predose (within 240 minutes before dosing) [a] | X |

Abbreviations: hh=hours mm=minutes; PK=pharmacokinetic

*a* Timepoint used in population PK analysis

## 11.2 PERIOPERATIVE SCHEDULE OF ASSESSMENTS

### 11.2.1 Definitions of minor and major surgery

Minor surgery is defined as any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated and does not meet the criteria for major surgery (eg, dental extraction of <3 non-molar teeth). Minor surgical procedures may be performed at a local health care provider institution.

Major surgery is defined as any invasive operative procedure that requires any of the following:

- Opening into a major body cavity (eg, abdomen, thorax, skull)
- Operation on a joint
- Removal of an organ
- Dental extraction of any molar teeth or ≥3 non-molar teeth
- Operative alteration of normal anatomy
- Crossing of a mesenchymal barrier (eg, pleura, peritoneum, dura)

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

### 11.2.2 Perioperative assessments of safety and hemostatic efficacy in patients undergoing major operative procedures

In patients undergoing major operative procedures during the fitusiran treatment period, safety and hemostatic efficacy assessments will be performed according to the Perioperative Schedule of Assessments (described below and outlined in Table 12, where possible).

After a review of medical and surgery history has been completed, patients will have the following assessed as specified in the Perioperative Schedule of Assessments (Table 12): directed physical examination and assessment of vital sign measurements; clinical laboratory assessments including hematology (complete blood count, white blood count, red blood cell count, hemoglobin, hematocrit, platelets); coagulation (APTT, PT/INR, fibrinogen, D-dimer); hepatic assessments; and hemostatic efficacy assessments (rating scale based on ISTH Scientific and Standardization Committee [SSC] definitions) (18).

**Table 12 - Perioperative schedule of assessments in patients undergoing major 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] | | | |
| 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, adverse events 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 7.6.3)
*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 7).
*g* If BPA administration and the surgical procedure occur at the study center visit, one sample should be collected pre-BPA administration and two samples should be collected post- BPA administration on the day the procedure. The pre- BPA sample may be collected any time before BPA administration. The post- BPA samples should optimally be collected at 10 min (±5 min) and 60 min (±10 min) after 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 BPA administration occurs at the study center visit, then assessments should be collected at the following time points: pre- BPA administration; 10 min (±5 min) post- BPA administration; and 60 minutes (±10 min) post- 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.

## 11.3 ISTH GUIDELINE FOR ASSESSMENT OF TREATMENT RESPONSE

ISTH recommendations (18) are provided in the table below for assessment of treatment response (Table 13).

**Table 13 - 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 14.

**Table 14 - 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 DATA PROTECTION

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

**Protection of participant data**

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

"Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant 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.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

**Protection of data related to professionals involved in the study**

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agency's disqualification list.

- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up to date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.

Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

## 11.6 COUNTRY-SPECIFIC REQUIREMENTS

### 11.6.1 United States

Change to the protocol for the United States only: new texts addition is presented as **bold** texts and deleted text is presented in ~~crossed~~ texts.

#### *11.6.1.1 Protocol synopsis*

Study design

The ATLAS-PPX trial (ALN-AT3SC-009 [Sanofi Genzyme EFC15110]) is a multicenter, multinational, 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, who have switched from prior bypassing agent (BPA, Cohort A) or factor (Cohort B) prophylaxis. A subgroup of Cohort A patients will include hemophilia B patients with inhibitory antibodies to Factor IX who are not responding adequately to BPA prophylaxis treatment (historical ABR ≥20). **U.S.A. patients can only participate in Cohort A.**

The study has 3 periods:

- 6-Month ~~factor or~~ BPA prophylaxis period in which patients will continue their prestudy, regularly scheduled prophylaxis regimen with ~~factor concentrates or~~ BPAs
  - The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this 6-month BPA prophylaxis period and will start the following period after the screening period.
- 1-Month onset period in which patients receive their first dose of fitusiran while continuing their ~~factor or~~ BPA prophylaxis for up to 7 days
- 6-Month fitusiran efficacy period in which patients receive fitusiran as prophylaxis

Together, the 1-month onset period and the 6-month fitusiran efficacy period constitute the fitusiran treatment period.

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

Following the screening and prophylaxis periods or following the screening period for the subgroup of Cohort A enrolling directly into the fitusiran treatment period, all patients will be treated with fitusiran for a total of 7 months. Because the full PD effect of fitusiran is not achieved until approximately 28 days after receiving the first dose, **for the US** efficacy will be assessed **not only during the overall treatment period (Day 1 to Day 190; primary endpoint), but also during the efficacy period (Day 29 to Day 190;** ~~final 6 months of the fitusiran treatment period (Day 29 to Month 7)~~ **key secondary endpoint).**

Throughout the study, patients may receive on-demand treatment for breakthrough bleeding episodes with ~~factors or~~ BPAs, as appropriate.

Number of planned patients

Approximately 80 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 50 patients without inhibitors (Cohort

B). Approximately 18 patients with hemophilia B (including approximately 7 hemophilia B patients in Cohort A, among which are a subgroup of no more than 4 patients who are not responding adequately to BPA prophylaxis)**,** 11 hemophilia B patients in Cohort B, and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment. **In the US, only patients from Cohort A will be included**.

Diagnosis and main eligibility criteria

~~Patients without inhibitors must have used factor concentrates for prophylaxis for at least the last 6 months prior to Screening and must meet each of the following criteria: 1) Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening, AND 2) No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening, AND 3) No history of immune tolerance induction therapy within the last 3 years prior to Screening. A minimum of 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening is required.~~

Reference therapy, dose and mode of administration

During the ~~factor or~~ BPA prophylaxis period, patients will continue ~~FVIII, FIX, or~~ BPA prophylaxis as treatment for hemophilia on a regimen consistent with recommendations in the approved prescribing information, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding. Dose and mode of administration will be per Investigator discretion; bleeding episode management should be per the local standard practice for episodic use of ~~factors or~~ BPAs and as per Investigator discretion. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate into this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. All patients will continue to receive ~~FVIII, FIX, or~~ BPA prophylaxis for the first 7 days of the onset period. Subsequently, breakthrough bleeding episodes will be treated with on demand ~~factor or~~ BPA therapy as necessary per the bleeding episode management guidelines.

Statistical methods

The primary endpoint ~~secondary endpoints (spontaneous bleeding episodes and joint bleeding episodes)~~ will be based on the bleeding events occurring in the ~~factor or~~ BPA prophylaxis period (Day -162 to Day -1), and the fitusiran **treatment period** (Day 1 to Day 190). To avoid confounding treatment effect, bleed data following major surgery, antithrombin administration, major trauma, or the re-initiation of prophylaxis treatment with ~~factors or~~ BPAs after fitusiran discontinuation will be excluded from the primary analysis.

The number of bleeding episodes will be analyzed using a repeated measures negative binomial model with fixed effect of treatment period. The logarithm of bleeding episode follow-up time in each period for each patient will be used as an offset parameter in the model to account for any difference in follow-up duration. The ratio of bleeding rates in the fitusiran ~~efficacy~~ **treatment period** relative to the factor/BPA prophylaxis period and its 95% CI and p-value will be presented. The p-value should be interpreted with caution. In addition, as a contrast Bayesian analyses will be performed to summarize the point estimates of the posterior probability of a

clinically significant treatment effect, along with associated measures of uncertainty. In addition, estimated mean ABR and its 95% CI during each of the 2 periods and during the fitusiran onset period and **efficacy period** (key secondary endpoint) will be presented.

**For the secondary endpoints**, the spontaneous bleeding episodes and the joint bleeding episodes will be analyzed using the same model as used in the primary analysis. ~~Safety data will be summarized descriptively.~~ The bleeding episodes in the fitusiran ~~onset period and in the fitusiran treatment~~ **efficacy** period will be analyzed using a negative binomial model with logarithm of follow-up time in the period as an offset parameter. Change in Haem-A-QOL physical health score and total score in the ~~factor~~/BPA prophylaxis period and fitusiran treatment period will be summarized descriptively. The annualized weight-adjusted consumption of ~~factor~~/BPA injections will be summarized using descriptive statistics.

**Safety data will be summarized descriptively.**

Table 1: Schedule of assessments

| | | ~~Factor or~~ BPA Prophylaxis Period[a] | | | | | | Fitusiran Treatment Period[b] | | | | | | | | AT F/U[d,e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Onset Period[b] | | Efficacy Period | | | | | | |
| **Study Visit (Month)** | Screening[a] | Month -6[a] | Month -5[a] | Month -4[a] | Month -3[a] | Month -2[a] | Month -1[a] | Baseline | | Month 1 | | Month 2 | Month 3 | Month 4 | Month 5 | EOT Month 6 | EOS/ET[c,d] Month 7 | Month 8 |
| **Study Day (±Visit Window)** | -228 to -169 | Day -168 | Day -140 ±7 | Day -112 ±7 | Day -84 ±7 | Day -56 ±7 | Day -28 ±7 | Day 1 | Day 15 ±3 | Day 29 ±7 | Day 43 ±3 | Day 57 ±7 | Day 85 ±7 | Day 113 ±7 | Day 141 ±7 | Day 169 ±7 | Day 197 ±7 | Day 225 ±7 |

Footnote "a": Routine prophylaxis with ~~factor concentrates or~~ BPAs for treatment of hemophilia. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in the BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. For these patients, the screening period will be from Day -60 to Day 0 and assessments during the BPA prophylaxis period are not applicable.

Footnote "b": Fitusiran as prophylaxis treatment and permitted on-demand use of ~~factors or~~ BPAs for treatment of breakthrough bleeding episodes. Patients may continue their routine ~~factor or~~ BPA administration schedule for up to the first 7 days of the onset period.

Footnote "m": To be performed in all patients, at any clinic visit during their ~~factor or~~ BPA prophylaxis period, with blood drawn before, 10 min (±5 min) after, and 60 min (±5 min) after administration of their usual prophylactic dose of ~~factor or~~ BPA. Laboratory testing pre- and post-~~factor~~/BPA include: Coagulation, and TG. The timing of this visit should coincide with the patient's usual prophylaxis regimen, so that pre-dose thrombin generation is at nadir and the benefit of administered ~~factor or~~ BPA is maintained.

Footnote "t": It is strongly preferred that ~~factor or~~ BPA administration and bleeding events are entered in the eDiary immediately or within 24 hours. Additional patient follow-up may be required as described in Section 7.2.1. Patients in the fitusiran treatment arm who present in the clinic with symptoms characteristic of a potential bleeding episode should have assessments completed per Table 2.

Table 2: Bleeding episode assessments - unscheduled visit

| | Predose | Postdose 10 min (±5 min)[d] | Postdose 60 min (±5 min) [d] |
|---|---|---|---|
| Directed Physical Examination[a] | X | | |
| Vital Signs | X | | |
| AT | X | | |
| ~~FVIII/FIX Levels (only if treated with FVIII or FIX)~~ | ~~X~~ | ~~X~~ | ~~X~~ |
| TG | X | X | X |
| Coagulation | X | X | X |
| Hematology | X | X | X |
| Optional Imaging[c] | X | | |

Abbreviations: AT=antithrombin; ~~FVIII=Factor VIII; FIX=Factor IX;~~ TG=thrombin generation

*a* See Section 7.6.3 for assessments to be performed during a directed physical examination.

*b* Removed.

*c* Investigator to consider confirmation of bleed via ultrasound or other imaging modality at clinical study centers where appropriate equipment and staff with related expertise is available.

*d* If the patient presents following administration of ~~factor or~~ BPAs at home and within 48 hours of the dose, and no further treatment is given at the center, AT and the postdose assessments should be obtained in a single draw at any time during the visit.

### *11.6.1.2 Protocol body*

Section 1.3 Study Design Rationale

The ATLAS-PPX trial (Alnylam ALN-AT3SC-009 [Sanofi Genzyme EFC15110]) is a multicenter, multinational, open-label Phase 3 switching study designed to demonstrate the efficacy and safety of fitusiran in patients with hemophilia A or B, who are currently treated with prophylactic regimens of ~~factor concentrates or~~ BPAs.

The switching design allows for an intra-patient control to enable examination of the effect of the two treatment methods through comparison of the median ABR during the ~~factor or~~ BPA prophylaxis period and the median ABR of the same patient group when receiving fitusiran, while limiting confounding effects of different patient bleeding phenotypes and prophylaxis therapy variability. Inhibitor patients with hemophilia B may have a high unmet need despite prophylactic BPA therapy, with limited other treatment options. Therefore, a limited number of inhibitor patients with hemophilia B who are not adequately responding to prophylactic BPA therapy could enroll directly into the fitusiran treatment period, thereby skipping the 6-month BPA prophylaxis period. 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.

Given that the study design employed is a single treatment arm, with a switch from prophylaxis to fitusiran for each patient, the study is not blinded. The primary endpoint of the study is ABR in the fitusiran efficacy period and the ~~factor or~~ BPA prophylaxis period. ABR is a well-established endpoint that has been used as the primary endpoint in global approvals of factor

replacement and BPA products. Secondary endpoints characterize annualized spontaneous and joint bleeding rates, change in Haem-A-QoL physical health score and total score in patients ≥17 years of age, ABR in the onset period, overall safety profile and the consumption of ~~factor/~~BPA.

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, has been used in other hemophilia clinical trials, has been validated, reviewed by clinicians, and is considered the most appropriate HRQOL tool available for use in the 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 (12).

In the event of a breakthrough bleeding episode, on-demand use of ~~factors or~~ BPAs will be permitted throughout the entire study duration (see Section 6.3.2).

Section 1.5 Benefit-Risk Assessment

Identified risks of fitusiran include serious vascular thrombosis, liver transaminase abnormalities, cholecystitis, and symptomatic cholelithiasis. In addition, serious hypersensitivity reactions, including injection site reactions, are considered a potential risk of fitusiran. The risk of vascular thrombotic events is thought to be elevated in patients receiving fitusiran with AT activity levels <10%. In addition, the concomitant treatment of breakthrough bleeding episodes with ~~factor or~~ BPA, due to particularly at doses higher than recommended in the protocol, may confer an increased risk of thrombotic events. Additional details regarding the benefits and risks of fitusiran are provided 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 a change in the fitusiran dosing regimen to minimize the occurrence of AT levels <10% (Section 6.2.3.2), detailed guidance and oversight on treatment of breakthrough bleeding episodes with reduced ~~factor and/or~~ BPA dosing (Section 6.3.2), and monitoring and management of thrombosis while patients are on fitusiran (Section 6.5). 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).

Section 2 Objectives

2.1. Primary Objective

- To characterize the frequency of bleeding episodes while receiving fitusiran treatment, relative to the frequency of bleeding episodes while receiving ~~factor concentrate or~~ bypassing agent (BPA) prophylaxis

2.2. Secondary Objectives

- To characterize the following while receiving fitusiran treatment, relative to receiving ~~factor or~~ BPA prophylaxis:
  - the frequency of spontaneous bleeding episodes
  - the frequency of joint bleeding episodes
  - health related quality of life (HRQOL) in patients ≥17 years of age
  - the consumption of ~~factor/~~BPA
- To characterize the frequency of bleeding episodes during the onset and **efficacy** periods in patients receiving fitusiran
- To characterize safety and tolerability of fitusiran

2.3. Exploratory Objectives

- To characterize the effects of fitusiran on the following patient reported outcomes while receiving fitusiran treatment, relative to receiving ~~factor or~~ BPA prophylaxis:
  - Patient satisfaction with fitusiran
  - Patient activity
  - HRQOL in adolescents (≥12 to <17 years of age)
- To characterize the pharmacodynamic (PD) effect, PK, and immunogenicity of fitusiran
- To characterize the effects of fitusiran on joint status while receiving fitusiran treatment, relative to receiving ~~factor or~~ BPA prophylaxis
- To characterize the effects of fitusiran on patient resource use, relative to receiving ~~factor or~~ BPA prophylaxis

Section 3 Endpoints

3.1 Primary Endpoint

- Annualized Bleeding Rate (ABR) in the fitusiran **treatment** ~~efficacy~~ period and ~~factor or~~ the BPA prophylaxis period

**3.2 Key secondary endpoint**

- **ABR in the fitusiran efficacy period**

3.3 Secondary Endpoints

- Annualized spontaneous bleeding rate in the fitusiran efficacy period and the ~~factor or~~ BPA prophylaxis period
- Annualized joint bleeding rate in the fitusiran efficacy period and the ~~factor or~~ BPA prophylaxis period
- Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period
- ABR in the onset period
- ~~ABR in treatment efficacy period~~
- Annualized weight-adjusted consumption of ~~factor/~~BPA

Section 4.1 Summary of Study Design

The ATLAS-PPX trial (ALN-AT3SC-009) is a multicenter, multinational, open label, Phase 3 study designed to characterize the efficacy and safety of fitusiran in male patients, aged ≥12 years, with severe hemophilia A or B, previously receiving ~~factor or~~ BPA prophylaxis. The study consists of ~~2 cohorts: C~~cohort A ~~will consist~~ of patients with inhibitory antibodies to Factor VIII or Factor IX~~; Cohort B will consist of patients without inhibitor antibodies to Factor VIII or Factor IX~~. A subgroup of Cohort A patients will include hemophilia B patients with inhibitory antibodies to Factor IX who are not responding adequately to BPA prophylaxis treatment (historical ABR ≥20) (see Inclusion Criteria in Section 5.1). **In the US only Cohort A will be enrolled.** The study has 3 periods defined by type of prophylaxis regimen:

- 6-Month ~~factor or~~ BPA prophylaxis period in which patients will continue their prestudy, regularly scheduled prophylaxis regimen with BPAs
  - The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this 6-Month BPA prophylaxis period and will start the following period after the screening period.
- 1-Month onset period in which patients receive first dose of fitusiran while continuing their ~~factor or~~ BPA prophylaxis for up to 7 days
- 6-Month fitusiran efficacy period in which patients receive fitusiran as prophylaxis.

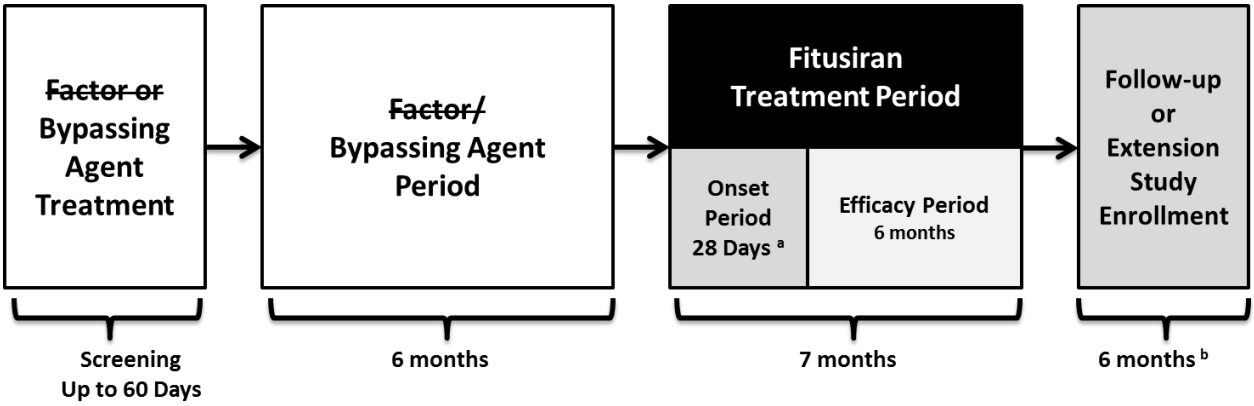
Together, the 1-month onset period and the 6-month fitusiran efficacy period constitute the fitusiran treatment period.

Bleeding events and doses of ~~factor concentrates or~~ BPAs 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.

On-demand use of ~~factor concentrates or~~ 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 period may receive on-demand treatment for breakthrough bleeding episodes with ~~factors or~~ BPAs, as appropriate. For patients in the fitusiran treatment period 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 6.3.2 per Investigator discretion.

**Following the screening and prophylaxis period, or following the screening period for the subgroup of Cohort A enrolling directly into the fitusiran treatment period, all patients will be treated with fitusiran for a total of 7 months. 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 remaining 6 months of the fitusiran treatment period (Day 29 to Month 7; key secondary endpoint). Therefore, the overall fitusiran treatment period is defined as the onset period (Day 1- 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).**

Figure 1: Study design



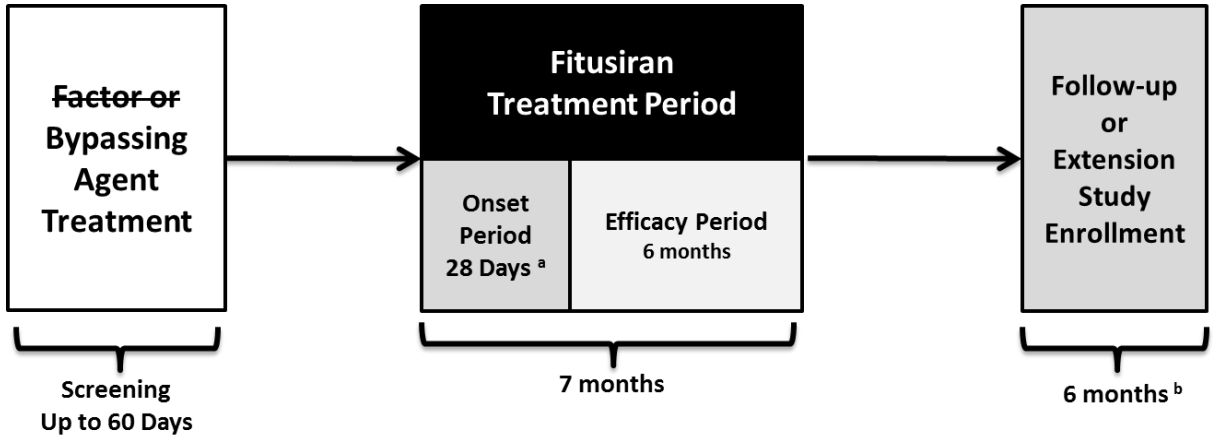

Abbreviations: AT=antithrombin

**Note: For subgroup of Cohort A patients enrolling directly into the fitusiran treatment period, see Figure 2.**

*a* Patients will continue to receive prescribed ~~factor or~~ BPA prophylaxis for the first 7 days of the onset period.

*b* Following final fitusiran dose, 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.

**Figure 2: Study design (for subgroup of Cohort A patients enrolling directly into the fitusiran treatment period)**




Abbreviations: AT=antithrombin

*a* Patients will receive prescribed ~~factor or~~ BPA prophylaxis for the first 7 days of the onset period.

*b* Following final fitusiran dose, 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.

Section 4.3 Number of Patients

Approximately 80 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 50 patients without inhibitors (Cohort B). Approximately 18 patients with hemophilia B (including approximately 7 hemophilia B patients in Cohort A, among which are a subgroup of no more than 4 patients who are not responding adequately to BPA prophylaxis [see Section 5.1]), and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment. **In the US, only patients from Cohort A will be included.**

Section 5.1 Inclusion Criteria

I 03. A minimum of 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening for patients with inhibitory antibodies to Factor VIII or Factor IX (Cohort A). ~~A minimum of 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening for patients without inhibitory antibodies to Factor VIII or Factor IX (Cohort B).~~

I 04. Must meet ~~either~~ the definition of inhibitor ~~or non-inhibitor~~ patient as below:

~~Inhibitor:~~

Use of BPAs for prophylaxis and for any bleeding episodes for at least the last 6 months prior to Screening, and meet one of the following Nijmegen-modified Bethesda assay results criteria:

- Inhibitor titer of ≥0.6 BU/mL at Screening, or

- Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of 2 consecutive titers ≥0.6 BU/mL, or
- Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of anamnestic response
- The subgroup of patients in Cohort A patients must additionally meet the following criteria to be eligible to start treatment with fitusiran directly after the screening period:
  - Hemophilia B with inhibitory antibody to Factor IX as defined above
  - Not responding adequately to BPA treatment (historical ABR ≥20) prior to enrollment
  - In the opinion of the Investigator, with approval of Sponsor Medical Monitor, 6-month BPA prophylaxis period should be omitted.

~~Non-inhibitor:~~

~~Use of factor concentrates for prophylaxis and for any bleeding episodes for at least the last 6 months prior to Screening, and meet each of the following criterion:~~

- ~~Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening and~~
- ~~No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening and~~
- ~~No history of immune tolerance induction therapy within the past 3 years prior to Screening.~~

I 05. Prescribed prophylactic treatment (documented in the medical or pharmacy records) of hemophilia with factor concentrates or BPAs for at least 6 months prior to Screening; the regimen must be consistent with the approved prescribing information for the product or local recommendations, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding.

Section 5.2 Exclusion Criteria

E 18. Completion of a surgical procedure within 14 days prior to Screening, or currently receiving additional ~~factor concentrate or~~ BPA infusion for postoperative hemostasis.

Section 5.3 Removal from Therapy or Assessment

Patients or their legal guardian (in case patient is a minor) are free to discontinue treatment or withdraw from the study at any time and for any reason, without penalty to their continuing medical care. Any discontinuation of treatment or withdrawal from the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator. The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest.

Patients who discontinue their prophylactic treatment or withdraw consent during the ~~factor or~~ BPA prophylaxis period (BPA prophylaxis period is not applicable for the subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment) will be withdrawn from the study.

Procedures for discontinuation of study drug and/or withdrawal from the study during the fitusiran treatment period are described in Section 5.3.1 and Section 5.3.2, respectively.

Section 6.3.1 ~~Factor Concentrates or~~ Bypassing agent prophylaxis

Section 6.3.1.1 Routine use of ~~factor or~~ bypassing agent prophylaxis in the ~~factor or~~ bypassing agent prophylaxis period

During the ~~factor or~~ BPA prophylaxis period, patients will continue to receive prophylaxis with their usual products on a regimen consistent with recommendations in the approved prescribing information, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding. The regimen used during the ~~factor or~~ BPA prophylaxis period must have a minimum frequency of administration as presented in Table 4. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period.

**Table 15 - ~~Factor or~~ Bypassing agent prophylaxis requirements**

| Type of ~~Factor or~~ BPA replacement | Frequency of administration |
|---|---|
| ~~Standard half life FVIII~~ | ~~Twice weekly~~ |
| ~~Extended half life FVIII~~ | ~~Once weekly~~ |
| ~~Standard half life FIX~~ | ~~Once weekly~~ |
| ~~Extended half life FIX~~ | ~~Once biweekly~~ |
| aPCC | Twice weekly |
| rFVIIa | Every other day |

Abbreviation: aPCC= activated prothrombin complex concentrates; BPA=bypassing agent; ~~FVIII = Factor VIII; FIX = Factor IX;~~ rFVIIa=recombinant Factor VIIa

Section 6.3.1.2 Management of ~~factor or~~ bypassing agent prophylaxis during the transition to the fitusiran treatment period

The first 28 days of fitusiran treatment is referred to as the onset period. During the onset period AT lowering will be progressing toward therapeutic levels. Patients will continue ~~factor or~~ BPA prophylaxis with minimum frequency as in Table 4, for the first 7 days of the fitusiran onset period. Subsequent to Day 7 of the fitusiran treatment period, ~~factor concentrates or~~ BPAs should be administered only for bleeding episodes or if needed in advance of invasive medical procedures.

Section 6.3.2 Management of bleeding episodes

The occurrence of bleeding episodes is a typical characteristic of hemophilia; [2, 7, 8] bleeding episodes will be recorded as efficacy assessments of fitusiran and will not be considered as AEs unless the criteria for SAEs are met (see adverse events definitions in Section 7.5.6.1). Bleeding episodes will be recorded in the eDiary. For bleeding episodes in which there was no ~~factor or~~ BPA infusion or other type of intervention employed, the reason the bleeding episodes were untreated will be recorded in the eDiary (see Section 7.2.1).

Investigators will establish and provide instructions for an individualized bleed management plan based on the guidelines in Table 5 for each patient.

The bleed management plan should be reviewed by the Investigator or designee with the patient at each clinic visit (and contact every 2 weeks between clinic visits) and updated as necessary.

Section 6.3.2.1 Bleeding episode management recommendations for patients during the ~~factor or~~ bypassing agent prophylaxis period (patients not receiving fitusiran)

During the ~~factor or~~ BPA prophylaxis period, bleeding management therapy with ~~factors or~~ BPAs will be managed based on the local standard practice for treating hemophilia patients **with inhibitors**, as routinely administered by the physician. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. Where clinical circumstances allow, it is recommended that the patient contact the Investigator for all events that may be suspected to be or are characteristic of a bleeding episode. If adequate hemostasis does not occur after two doses of ~~factor or~~ BPA, the patient should contact the site for further instruction. If the patient feels the need to administer doses higher than the patient's bleeding episode management plan recommends, or at a higher frequency, it is recommended that the patient contact the site. See Section 7.2.1 regarding patient use of the eDiary and site alerts that will assist in this process.

Section 6.3.2.2 Bleeding episode management recommendations for patients during the fitusiran treatment period

Given the mechanism of action and pharmacodynamics profile of fitusiran, the ~~factor or~~ BPA dose necessary to safely and effectively treat breakthrough bleeding episodes in patients receiving fitusiran during the fitusiran treatment period will be lower than standardly prescribed. This is supported by data from the Phase 1 study in which bleed events were managed with factor or BPA, as well as additional modeling and ex vivo spiking data. More detailed information on the clinical experience in bleeding episode management in Phase 1 and Phase 1/2 fitusiran studies, as well as supportive nonclinical studies is provided in the Investigator's Brochure.

After administration of fitusiran, AT lowering will be progressing toward therapeutic levels. As quickly as 7 days after the initial fitusiran dose, the majority of patients will have AT levels at or below 60% residual activity. By 14 days after dosing, it is expected that 94% of patients will have AT lowering of >50%, with a median value of 66.8%. Based on these AT kinetics, it is recommended that patients continue with their standard ~~factor or~~ BPA regimens for the

first 7 days following initiation of fitusiran dosing, with institution of the protocol-specific bleed management guidelines with reduced ~~factor or~~ BPA at Day 8 and beyond (Table 5).

Patients on fitusiran will be provided a written bleed management plan with appropriate dosing of ~~factor or~~ BPA for use during Day 1 through 7, as well as a bleed management plan with dosing for Day 8 and beyond. Thereafter the bleed management plan will be reviewed and updated at monthly visits, and new written plans provided to the patient if dosing changes.

Importantly, after Day 7 of the fitusiran treatment period, patients should not use ~~factor,~~ BPA, or other hemostatic agents as prophylaxis for bleeding episode prevention, including doses related to anticipated hemostatic challenges such as physical activity. For prophylaxis of bleeding episodes in patients who require operative procedures see Section 6.6.

**Bleed Management Guidelines Day 1 to Day 7 of Fitusiran Treatment Period:**

Patients should be instructed to call the site prior to administering ~~factor or~~ BPA for the management of bleeding episodes. Patients should continue with their standard ~~factor or~~ BPA regimens.

**Bleed Management Guidelines Day 8 and Beyond of Fitusiran Treatment Period:**

When a patient experiences symptoms that may be consistent with bleeding episodes, the following steps should be followed:

1. Patient should be instructed to call the study center to discuss symptoms to determine whether or not they are consistent with a bleeding event and to discuss the appropriate ~~factor and/or~~ BPA dose to use. This interaction between patient and Investigator is recommended prior to the administration of each dose of ~~factor or~~ BPA. Confirmation of bleeds at the study center prior to treatment may be considered. Such visits should capture assessments per Section 6.4 and Table 2.
2. If a determination is made that symptoms require treatment, the recommended treatment algorithm for bleeding episodes is described below:
    1. A single dose can be administered according to the guidelines in Table 5.
    2. The patient should be instructed to re-evaluate symptoms in 24 hours for bleeds treated with ~~FVIII, FIX or~~ aPCC and in 2-3 hours for bleeds treated with rFVIIa.
        a) Administration of FIX Extended half-life should not be more frequent than every 5-7 days.
    3. If a second dose (in the case of ~~FVIII, FIX or~~ aPCC) or a third dose (in the case of rFVIIa) is needed, the patient must call the study center before dosing.
        a) Consider evaluation and treatment of the patient at the study center and confirmation of bleeds when any repeated doses are needed (See Section 6.4 and Table 2).
        b) If more than two doses of ~~FVIII, FIX or~~ aPCC or three doses of rFVIIa are needed, the patient should be seen at the study center within 48-72 hours.

4. Doses should not be administered at less than 24-hour intervals (except rFVIIa as indicated in Table 5).
5. Doses should not exceed the protocol maximum recommended dose indicated in Table 5.
6. Consultation with the study Medical Monitor and Clinical Advisor should be considered for clinical circumstances below, that may warrant AT replacement:
   a) Doses of ~~factor or~~ BPA higher than those recommended in Table 5
   b) Dosing of ~~factor or~~ BPA at decreased intervals than those recommended in Table 5
   c) Multiple or repeated doses of ~~factor or~~ BPA
7. Antifibrinolytics may not be used in combination with ~~factor or~~ BPA.

**Table 16 - Bleed management dosing guidelines by specific product**

| | Factor VIII | Factor IX Standard half-life | Factor IX Extended half-life | aPCC | Recombinant Factor VIIa |
|---|---|---|---|---|---|
| **Recommended <u>single</u> dose of** | 10 IU/kg | 20 IU/kg | 20 IU/kg | 30 U/kg | ≤45 µg/kg |
| **Single Dose should not exceed** | 20 IU/kg | 30 IU/kg | 30 IU/kg | 50 U/kg | 45 µg/kg |
| **Repeat dose instructions** | Mandatory to call the clinical study center prior to second dose<br>Consider evaluation and treatment at the clinical study center<br>(see Section 6.4) | | | | Mandatory to call site prior to third dose |
| | Should not repeat in less than 24 hours | Should not repeat in less than 24 hours | Should not repeat in less than 5-7 days | Should not repeat in less than 24 hours | Should not repeat in less than 2 hours |
| | Should be seen at site within 48-72 hours if more than 2 doses are required<br>(see Schedule of Assessments Table 1 for assessments) | | | | Should be seen at site within 48-72 hours if more than 3 doses are required |
| | **For situations requiring higher doses, more frequent administration, multiple repeated doses, discussion with study Medical Monitor and Clinical Advisor is recommended, and AT replacement should be considered.**<br>Do not use antifibrinolytics in combination with factor or BPA. | | | | |

Note: **Doses of FVIII and FIX are included for completeness. It is expected that these non-inhibitor patients will be managed with factor concentrates and inhibitor patients will be routinely managed with rFVIIa or aPCC for bleeding episodes.** Adjunctive management of bleeding episodes should be carried out per standard of care.

Section 6.3.2.3 Use of ~~Factor or~~ Bypassing agents following discontinuation of fitusiran

**Resuming routine prophylaxis following discontinuation of fitusiran**

Patients who opt to discontinue fitusiran may resume standard prophylaxis with ~~factor concentrates or~~ BPAs when their AT activity level returns to approximately 60% (per the central laboratory). An earlier restart of standard treatment may be considered in conjunction with consultation from the study Medical Monitor, if a strong medical need arises (eg, increased frequency of bleeding).

**Bleed episode management following discontinuation of fitusiran**

Patients who opt to discontinue fitusiran may resume standard on-demand dosing with ~~factor concentrates or~~ BPAs for bleeding episodes when their AT residual activity level returns to approximately 60% (per the central laboratory). An earlier restart of standard treatment may be considered in conjunction with consultation from the study Medical Monitor, if a strong medical need arises (eg, increased frequency of bleeding). If full doses of ~~factor or~~ BPA are required to achieve hemostasis prior to AT recovery (approximately 60% residual activity per the central laboratory), AT replacement should be considered.

Section 6.5 Monitoring and Management of Thrombotic Events

Given safety events observed thus far and the possible thrombotic risk associated with fitusiran's AT lowering mechanism, which may be increased with concurrent use of ~~factor concentrates or~~ BPAs, there should be a low threshold to evaluate any signs and symptoms consistent with thrombosis, including symptoms consistent with CVST. Symptoms of thrombosis may include a severe or persistent headache, headache with nausea and vomiting, chest pain/tightness, coughing up blood, trouble breathing, abdominal pain, fainting or loss of consciousness, vision problems, and swelling or pain in the arms or legs.

If signs and symptoms consistent with thrombosis are present, the Investigator should evaluate the patient for thrombosis, including appropriate imaging studies. For the diagnosis of CVST magnetic resonance imaging venogram (MRV) or computed tomography venogram (CTV) are recommended (15).

If a patient develops a thrombosis while on fitusiran, AT reversal is recommended in combination with ~~factor or~~ BPA replacement and appropriate anticoagulation. AT reversal should follow labeled product recommendations for the prevention of perioperative thrombosis in patients with AT deficiency, and individualize patient doses to target 80-120% AT activity. The use of plasma derived AT may be preferable to recombinant AT, given its longer half-life. It is recommended that cases of thrombosis are discussed with the study Medical Monitor and Clinical Advisor (see Section 7.5.6.1 for further information regarding Adverse Events of Special Interest).

Section 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 ~13-months, except for patients in the subgroup of Cohort A, which is up to 7 months, of eDiary recording (including both the 6-month ~~factor or~~ BPA prophylaxis period [6-month BPA prophylaxis period is not applicable for the subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment] and 7-month fitusiran treatment period).

Section 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 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 ~~factor concentrate and/or~~ BPA prescriptions (in the medical or pharmacy record) and documentation of reported number of bleeding episodes over the last 6 months (for inhibitor patients) ~~or 12 months (for non-inhibitor patients)~~. 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 study 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).

Section 7.2 Efficacy Assessments

***Bleeding Episode Definitions***

A bleeding episode is defined as any occurrence of hemorrhage that requires administration of ~~factor or~~ BPA infusion, eg, hemarthrosis, muscle, or mucosal bleeding episodes. 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 (18).

The start time of a bleeding episode will be considered the time at which symptoms of 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 6.3.2.

### 7.2.1 Electronic Diary

Patients will be issued an eDiary to record all bleeding events and all doses of ~~factors or~~ 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 ~~factors or~~ BPAs, and reasons for dosing (prophylaxis, treatment of a bleeding episode, and preventive dose for anticipated activity). Training of patients should be documented in the appropriate source record.

The Sponsor will review diary entries for data quality to identify issues such as patients who may need retraining on eDiary 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) continuously for the study duration. The site will contact the patient at a minimum interval of every 2 weeks (± 4 days) per schedule of assessments to review eDiary 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 bleed. 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 ~~factor or~~ 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.

Section 7.3.3 Coagulation/Thrombin generation response assessment in ~~factor or~~ bypassing agent prophylaxis period

During the ~~factor or~~ BPA prophylaxis period (before fitusiran treatment), patients will undergo a coagulation and peak thrombin/thrombin generation response assessment with timed blood collections both before and following a dose of their routine ~~factor or~~ BPA prophylaxis doses. The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. For these patients, the coagulation and peak thrombin/thrombin generation response assessment are not applicable.

These laboratory assessments are collected for research purposes, will be run centrally, and will not be released to sites or used to guide study conduct or clinical management.

Section 7.5.5.1 Additional laboratory assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities during either the ~~factor or~~ BPA prophylaxis period (BPA prophylaxis period is not applicable for the subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment) or the fitusiran treatment period. Following the occurrence of elevated liver transaminases or other LFT abnormalities per the central laboratory, all assessments in Table 7 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, AT levels, and other assessments or evaluations per Investigator discretion, as appropriate.

Section 8.1 Determination of Sample Size

Sample size is based on clinical considerations. The overall sample size of 80 patients including approximately 30 patients with inhibitor (Cohort A) and approximately 50 patients without inhibitor (Cohort B) was selected recognizing the limited number of patients with hemophilia, and to yield a reasonably robust estimate of the fitusiran bleeding episode rate and address the secondary objectives, including characterization of safety and tolerability. The proposed sample size is also expected to provide reasonable precision around the ratio of bleeding rate in the

fitusiran ~~efficacy~~ **treatment** period to bleeding rate in the factor or BPA prophylaxis period for both Cohort A and Cohort B. **In the US, only patients from Cohort A will be included.**

Section 8.2.5.1 Primary endpoint

The primary analysis will be performed on the EAS and will include all bleeding episodes occurring in the factor or BPA prophylaxis period (Day -162 to Day -1) and the fitusiran **treatment** period (**Day** 1 to Day 190~~). If a patient does not have bleeding episode data collected after Day 28 (eg due to early study discontinuation), the available bleeding episode data starting from Day 1 will be used in the primary analysis~~. To avoid confounding the treatment effect, bleeding episode data during and after major surgery, antithrombin administration, major trauma, or initiation of prophylaxis treatment with factors or BPAs during the fitusiran treatment period will be excluded from the primary analysis.

The number of bleeding episodes will be analyzed using a repeated measures negative binomial model with fixed effect of treatment period. The logarithm number of days that each patient spends in the treatment period matching the bleeding episode data being analyzed will be included as an offset variable to account for unequal follow-up time due to early withdrawal or surgery. The ratio of bleeding rates in the fitusiran **treatment** period to the factor or BPA prophylaxis period and its 95% CI and p-value will be presented. The p-value should be interpreted with caution. In addition, as a contrast Bayesian analyses will be performed to summarize the point estimates of the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty. The estimated mean ABRs in these 2 periods along with their 95% CIs will be presented from this model. In addition estimated mean ABR and its 95% CI during the fitusiran onset period and efficacy period (key secondary endpoint) will be presented.

Section 8.2.5.2 Secondary endpoint

Spontaneous bleeding episodes and joint bleeding episodes will be analyzed using the same method as primary analysis of ABR. Summary statistics, including the median and interquartile range, for annualized spontaneous bleeding rate and annualized joint bleeding rate will be reported.

Change in Haem-A-QOL physical health score and total score (in patients ≥17 years of age) in the ~~factor or~~ BPA prophylaxis period and fitusiran treatment period will be summarized descriptively. A mixed model for repeated measures analysis may be performed as deemed appropriate.

The bleeding episodes in the fitusiran onset period and in the fitusiran treatment period will be analyzed using a negative binomial model with logarithm of follow-up time in the period as an offset parameter. Summary statistics, including the median and interquartile range, for the ABR in 2 periods will be reported.

The secondary endpoint of annualized weight-adjusted consumption of ~~factor/~~BPA injections will be summarized using descriptive statistics.

### 11.6.2 Japan

As recommended by the PMDA, the following sections are modified for Japan:

#### 6.3.2.2 Bleeding episode management recommendations for patients during the fitusiran treatment period

**Table 5 - Bleed management dosing guidelines by specific product**

Footnote Additions

The half-life of standard Factor VIII and Factor IX replacement therapies are approximately 12 hours and approximately 16-18 hours, respectively (16). The improvement in half-life of extended Factor VIII therapies are approximately 1.2- to 1.5-fold, whereas the improvement in half-life of extended Factor IX therapies are much greater at approximately 3 to 5 fold (17). Thus, given the shorter half life of standard Factor VIII therapies and the limited improvement in half life of extended Factor VIII replacement therapies, the product-specific recommendations for dosing frequency of Factor VIII apply to all standard half-life and extended half-life Factor VIII products.

Time periods indicated in the repeat dose instructions section of Table 6 of the protocol start at the time of the first injection.

Should AT reversal be considered, it is strongly recommended that cases be discussed with the study Medical Monitor and Clinical Advisor. Dosing of AT replacement therapies in Japan should follow locally available AT replacement therapies for the treatment of thrombogenicity tendency based on congenital AT deficiency targeting peak levels of 80-120% AT activity level. Timing of AT replacement should be determined by the clinical circumstances with avoidance of delays in standard treatment as dictated by clinical scenario. Antithrombin level should be monitored per AT label during dosing adjustments. Resumption of fitusiran following AT reversal will follow clinical circumstances and may include guidance from the Medial Monitor, Clinical Advisors and/or the Data Monitoring Committee (see Section 4.1 and Section 10.1.5).

### 6.5 Monitoring and Management of Thrombotic Events

If a patient develops thrombosis while on fitusiran, AT reversal is recommended in combination with factor or BPA replacement and appropriate anticoagulation. Antithrombin reversal should follow labeled product recommendations of locally available AT replacement therapy for treatment of thrombogenicity tendency based on congenital AT deficiency, and patient doses individualized to target 80-120% AT activity level. It is recommended that cases of thrombosis are discussed with the study Medical Monitor and Clinical Advisor (see Section 8.4 for further information regarding AEs of Specific Interest).

### 6.8 Contraceptive Requirements

Patients in this study upon consultation with their Investigators must agree to use appropriate contraceptive method(s) for 72 hours after each administration of the study drug.

## 6.11 Management of AT and rFVIIa in Japan (new section)

In Japan, relationship between AE/SAE and ATs administration for AT replacement is to be collected. Antithrombins will be supplied by the Sponsor. The supplied ATs will be stored appropriately, and the storage condition, date of administration, usage amount etc. will be recorded at study sites in the same manner as IMP.

In addition, relationship between AE/SAE and rFVIIa is also to be collected when rFVIIa is administrated on top of fitusiran. Nevertheless, rFVIIa will not be supplied by the Sponsor.

## 11.7 PROTOCOL AMENDMENT HISTORY

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

### 11.7.1 Amended Protocol 01

Primary changes:

- Change to the type of population studied, to only patients with inhibitors; planned sample size reduced to N=30; eligibility criteria updated to only include patients who have an inhibitory antibody to FVIII or FIX and must have an ABR of at least 4 (ie, 2 bleeds within past 6 months)
- 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 prophylactic and bleed management 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
- 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

### 11.7.2 Amended Protocol 02

**AMENDMENT 02 (31 May 2018)**

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**OVERALL RATIONALE FOR THE AMENDMENT**

Clinical development and commercialization of fitusiran were granted from Alnylam Pharmaceuticals, Inc. to Genzyme Corporation, a Sanofi Company that will be assuming responsibility of the current clinical program. Therefore, the Alnylam logo and reference to Alnylam within the confidentiality statement were deleted from the title page. Throughout all sections of the protocol including the page headers and appendices, Alnylam has been changed to “the Sponsor” or “Sanofi Genzyme” as appropriate. In addition to change in Sponsor name, address and contact details were also updated. The Sanofi Genzyme study code (EFC15110) has been added. The Alnylam study drug code ALN-AT3SC has also been updated to the generic drug name fitusiran. Sections regarding ‘Criteria for Study Termination’, ‘Study Drug Accountability’, ‘Guidelines for Reporting Product Complaints/Medical Device Incidents (Including Malfunctions)’, ‘Study Monitoring’, ‘Ethics’, ‘Data Handling and Record Keeping’, ‘Publication Policy’ and ‘Dissemination of Clinical Study Data’ have been created or updated to reflect the Sanofi Genzyme environment. The study is expanded to include non-inhibitor patients under prophylaxis with factor concentrates: while inhibitor patients have higher unmet needs compared to non-inhibitor patients, there is no known difference in risks between these 2 populations based on the mechanism of action of fitusiran or factor/BPA therapy.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Throughout | Name of Sponsor changed from "Alnylam Pharmaceuticals, Inc." to "Genzyme Corporation" | Change of protocol Sponsor |
| Title of the study (also relevant text updated throughout) | Changed from "ATLAS-PPX: an open-label, multinational, switching study to describe the efficacy and safety of fitusiran prophylaxis in patients with hemophilia A and B with inhibitory antibodies to factor VIII or IX previously receiving bypassing agent prophylaxis." to "ATLAS-PPX: an open-label, multinational, switching study to describe the efficacy and safety of fitusiran prophylaxis in patients with hemophilia A and B previously receiving factor or bypassing agent prophylaxis" | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Title page | IND number 125632 added | Study to be conducted at US sites |
| Title page | Disclaimer note text changed | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Title page | Name of Sponsor contact changed from "Pushkal Garg" to "Olivier Huynh-Ba" | Change of protocol Sponsor; contact details |
| Throughout | Name of product "ALN-AT3SC" changed to "Fitusiran" | Change of protocol Sponsor; name of product updated |
| Synopsis | Number of study centers updated from "60" to "70" | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Synopsis and Section 3.2 (Secondary Endpoints) and throughout relevant text | "Change in Haem-A-QOL score in the treatment period" changed to "Change in Haem-A-QOL physical health score and total score in the treatment period" | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Synopsis and Section 4.3 | Number of planned patients: Text updated from "Approximately 30 patients are planned for enrollment in this study, all with inhibitors, including approximately 7 patients with hemophilia B, and approximately 3 adolescents (≥12 to <18 years of age)" to "Approximately 70 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 40 patients without inhibitors (Cohort B). Approximately 18 patients with hemophilia B, and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment" | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis | Diagnosis and main eligibility criteria: Text added as "Patients without inhibitors must have used factor concentrates for prophylaxis for at least the last 6 months prior to Screening and must meet each of the following criteria: 1) Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening, AND 2) No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening, AND 3) No history of immune tolerance induction therapy within the last 3 years prior to Screening. A minimum of 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening is required." | Eligibility criteria amended to encompass patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Table 1 | Footnote "W" changed from: "Non-serious AEs will be monitored and recorded from date of Day 1 visit through Follow-Up. SAEs will be monitored and recorded from date of signed informed consent through Follow-Up. Signs and symptoms of thrombosis will be evaluated at every visit (see Section 6.5)" to "AEs will be monitored and recorded from date of signed informed consent through Follow-Up. Signs and symptoms of thrombosis will be evaluated at every visit (see Section 6.5)." | For consistency throughout the protocol |
| Table 2 | Table updated with FVIII and/or FIX level to be checked at 10 minutes and 60 minutes postdose. | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Throughout | "Investigational study drug" changed to "Investigational medicinal product" | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 1.3 (only at first occurrence) | "Sanofi Genzyme EFC15110" added to the Study number "ALN-AT3SC-009" | Change of protocol Sponsor; Sanofi Genzyme study ID required for administrative purposes on first use |
| Section 4.1 | Text added as "… previously receiving factor or BPA prophylaxis. The study consists of 2 cohorts: Cohort A will consist of patients with inhibitory antibodies to factor VIII or factor IX; Cohort B will consist of patients without inhibitor antibodies to factor VIII or factor IX." | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 4.1 (Figure 1) | Study design updated to reflect the inclusion of non-inhibitor patients. | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Synopsis and Section 4.2 | Duration of treatment language updated | For clarity |
| Section 5.1 | Inclusion criterion #3 updated from "A minimum of 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening" to "A minimum of 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening for patients with inhibitory antibodies to factor VIII or factor IX (Cohort A). A minimum of 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening for patients without inhibitory antibodies to factor VIII or factor IX (Cohort B)." | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Section 5.1 | Inclusion criterion #4 updated with definition of non-inhibitor patients. | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Section 6.2.6 | "Accountability" section updated with reporting procedure to follow with regards to any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 6.3.1.1 (Table 4) | Table updated with details of standard and extended half-life of factor VIII and factor IX | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Section 6.3.2.2 (Table 5) | Footnote updated | Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX |
| Throughout | "Adverse events of clinical interest" changed to "Adverse events of special interest" | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 7.5.6.1 | Systemic injection associated reactions (IARs) added to the criteria of adverse events of special interest | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 7.5.6.2 | "Recording adverse events" section updated | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 7.5.6.3 | Heading updated from "Serious Adverse Events Require Immediate Reporting to | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Sponsor/Designee" to "Serious Adverse Events and Adverse Events of Special Interest Require Immediate Reporting to Sponsor/Designee" | |
| Section 7.5.6.7 | Overdose reporting text updated | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 7.5.6.8 | New Section 7.5.6.8 "Guidelines for Reporting Product Complaints/Medical Device Incidents (Including Malfunctions)" added with text | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 8.1 | Text updated for sample size with new Table 9 added for simulated ratio of rates for Cohort A, with 95% confidence intervals | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Synopsis and Section 8.2 | Text added "These analyses will be done for Cohort A and Cohort B separately. A pooled analysis will be performed after all patients in the 2 cohorts have either finished the Month 7 visit during the fitusiran treatment period or discontinued from the study". | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 8.2.5.1 | Text changed from "The primary analysis will be performed on the EAS and will include all bleeding episodes occurring in the factor or bypass agent prophylaxis period (Day -162 to Day -1) and the fitusiran efficacy period (Day 29 to Day 190) including bleeding episode data collected after discontinuation of study drug" to "The primary analysis will be performed on the EAS and will include all bleeding episodes occurring in the factor or bypass agent prophylaxis period (Day -162 to Day -1) and the fitusiran efficacy period (Day 29 to Day 190)". | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 8.2.10 | Text changed from "No interim analysis is planned" to "An Interim Analysis may be conducted as a part of this study". | An interim analysis may be conducted as a part of this study to support regulatory filings. |
| Section 9.1 | Ethical and Regulatory Considerations language updated to provide additional details | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 9.1.1 | Informed Consent Process language updated to provide additional process details and clarity | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 9.1.2 | Ethical Review language updated for clarity | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 9.1.3 | Study Documentation, Confidentiality, and Records Retention language updated | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 9.1.5 | Discontinuation of the Clinical Study language updated | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 9.2.1 | Data Handling language updated to provide additional details and clarify responsibilities | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 9.2.2 | Study Monitoring language updated to provide more detail regarding source data verification and record retention | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 9.3 | Publication Policy language updated to provide additional process details and some text moved into Section 9.4 | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Section 9.4 | New Section 9.4 “Dissemination of Clinical Study Data” added with text | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Appendix 11 | Appendix 11.5 - appendix for Country-Specific Requirements and Appendix 11.6 - appendix for protocol amendment history added | Change of protocol Sponsor; text aligned with Sanofi Genzyme environment |
| Throughout | Minor editorial, typo error corrections and document formatting revisions | Minor, therefore have not been summarized |

### 11.7.3 Amended Protocol 03

**AMENDMENT 03 (24 August 2018)**

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**OVERALL RATIONALE FOR THE AMENDMENT**

This is the Republic of Ireland-specific protocol amendment to allow a subgroup of Cohort A patients with hemophilia B with inhibitory antibodies to Factor IX who are not responding adequately to bypassing agent (BPA) prophylaxis treatment (defined as annualized bleeding rate ≥20) to start treatment with fitusiran directly after the screening period.

Inhibitor patients with hemophilia B may have a high unmet need despite prophylactic BPA therapy, with limited other treatment options. Therefore, a limited number of inhibitor patients with hemophilia B who are not adequately responding to prophylactic BPA therapy could enroll in the ALN-AT3SC-009 (Sanofi Genzyme EFC15110) study directly into the fitusiran treatment period, thereby skipping the 6-month bypassing agent treatment period.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title page | Added WHO number: U1111-1217-3270 | Administrative change |
| Synopsis (Study Design) | Changed from "……who have switched from factor (Cohort A) or bypassing agent (BPA, Cohort B) prophylaxis." to ".... who have switched from prior bypassing agent (BPA, Cohort A) or factor (Cohort B) prophylaxis." | Corrected the typographical error. |
| Synopsis (Study Design, Number of Planned Patients, Diagnosis and Main Eligibility Criteria, Reference Therapy, Dose and Mode of Administration, Duration of Treatment) | Following sentence added at appropriate location of these sections: "For the Republic of Ireland specific requirements, see Appendix 11.5.1.1" | This is the Republic of Ireland-specific protocol amendment to allow a subgroup of Cohort A patients to start treatment with fitusiran directly after the screening period. |
| Table 1: Schedule of Assessments | Following sentence added at the end of footnote "a": "For the Republic of Ireland specific requirements, see Appendix 11.5.1.1" | This is the Republic of Ireland-specific protocol amendment to allow a subgroup of Cohort A patients to start treatment with fitusiran directly after the screening period. |
| Section 1.3 Study Design Rationale<br>Section 4.1 Summary of Study Design<br>Section 4.2 Duration of Treatment<br>Section 4.3 Number of Patients<br>Section 5.1 Inclusion Criteria (criterion 4)<br>Section 5.3 Removal from Therapy or Assessment<br>Section 6.3.1.1 Routine Use of Factor or Bypassing Agent Prophylaxis in the Factor or Bypassing Agent Prophylaxis Period<br>Section 6.3.2.1 Bleeding Episode Management Recommendations for Patients during the Factor or Bypassing Agent Prophylaxis Period (Patients Not Receiving Fitusiran)<br>Section 6.9 Treatment Compliance<br>Section 7.3.3 Coagulation/Thrombin Generation Response Assessment in Factor or Bypassing Agent Prophylaxis Period<br>Section 7.5.5.1 Additional Laboratory Assessments | Following sentence added at appropriate location of these sections: "For the Republic of Ireland specific requirements, see Appendix 11.5.1.2" | This is the Republic of Ireland-specific protocol amendment to allow a subgroup of Cohort A patients to start treatment with fitusiran directly after the screening period. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Appendix 11.5 | Republic of Ireland-specific requirements have been added. The changes are identified in the Appendix 11.5.1. | This is the Republic of Ireland-specific protocol amendment to allow a subgroup of Cohort A patients to start treatment with fitusiran directly after the screening period. |
| Appendix 11.6.2 | Newly added appendix. Texts from the "Document History" page have been moved to this appendix. | Due to change in the amendment number, overall rationale and summary of changes of protocol amendment 02 have been moved to Appendix 11.6.2. |

### 11.7.4 Amended Protocol 04

**AMENDMENT 04 (18 December 2018)**

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**OVERALL RATIONALE FOR THE AMENDMENT**

Global changes:

Inhibitor patients with hemophilia B may have a high unmet need despite prophylactic BPA therapy with limited other treatment options. Therefore, a limited number of inhibitor subjects with hemophilia B, who are not adequately responding to prophylactic BPA therapy could enroll directly into the fitusiran treatment period of the ALN-AT3SC-009 STUDY (Sanofi Genzyme EFC15110), thereby skipping the 6-month bypassing agent treatment period.

In the Republic of Ireland, Amendment 03 of the protocol includes a subgroup of Cohort A subjects with hemophilia B (with inhibitory antibodies to Factor IX, who are not responding adequately to BPA prophylaxis (treatment defined as ABR ≥20) to start treatment with fitusiran directly after the screening period. The purpose of this global amendment, is to extend worldwide the inclusion of this subgroup, limiting however the inclusion to up to 4 patients.

A secondary objective and endpoint are included to further assess fitusiran efficacy.

United Stated specific requirement: Primary rationale for amendment:

In order to address the regulatory requirement from the US Food and Drug Administration (FDA), the US population for this study will be limited to patients with inhibitory antibodies to Factor VIII or Factor IX with more than 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening.

Japan specific requirements:

Specific requirements for Japan who were previously managed through protocol addendum and administrative changes are now included in the protocol.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis (Study Design, Number of Planned Patients, Diagnosis and Main Eligibility Criteria, Reference Therapy, Dose and Mode of Administration, Duration of Treatment) | Following sentence removed: "For the Republic of Ireland specific requirements, see Appendix 11.5.1.1" | Since the Republic of Ireland amendment is extended to the global protocol, it is no longer specific to the Republic of Ireland. |
| Synopsis (Study Design, Number of Planned Patients, Diagnosis and Main Eligibility Criteria, Reference Therapy, Dose and Mode of Administration, Statistical Methods) | Following sentence added at appropriate location of these sections: "For the United States specific requirements, see Appendix 11.5.1.1" | This is the United States specific protocol amendment to limit the enrollment to patients with inhibitory antibodies to Factor VIII or Factor IX. |
| Synopsis: Objectives | "To characterize the annualized weight-adjusted consumption of factor/BPA while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis" is added as a secondary objective | A secondary objective and endpoint are included to further assess fitusiran efficacy. |
| Synopsis: Endpoints | Secondary endpoint "Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period" is changed to "Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period" | Correction of a discrepancy with the corresponding study objective. |
| Synopsis: Endpoints | "Annualized weight-adjusted consumption of factor/BPA" is added as a secondary endpoint | A secondary objective and endpoint are included to further assess fitusiran efficacy. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis: Study Design | Following sentences added at appropriate location: "A subgroup of Cohort A patients will include hemophilia B patients with inhibitory antibodies to Factor IX who are not responding adequately to BPA prophylaxis treatment (historical ABR ≥20)." and "The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in this 6-month BPA prophylaxis period and will start directly receiving fitusiran (in the 1-month onset period described below) after the screening period.<br>The following sentence "Following the screening and prophylaxis periods, all patients will be treated with fitusiran for a total of 7 months and will receive 7 SC injections of fitusiran." is changed to "Following the screening and prophylaxis periods, or following the screening period for the subgroup of Cohort A enrolling directly into the fitusiran treatment period, all patients will be treated with fitusiran for a total of 7 months and will receive 7 SC injections of fitusiran." | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |
| Synopsis: Number of Planned Patients | Following sentence "30 patients with inhibitors (Cohort A) and approximately 40 patients without inhibitors (Cohort B). Approximately 18 patients with hemophilia B and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment." changed to "30 patients with inhibitors (Cohort A) and approximately 40 patients without inhibitors (Cohort B). Approximately 18 patients with hemophilia B (including approximately 7 hemophilia B patients in Cohort A, among which are a subgroup of no more than 4 patients who are not responding adequately to BPA prophylaxis and approximately 11 hemophilia B patients in Cohort B), and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment." | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis: Diagnosis and Main Eligibility Criteria | Following sentence added at appropriate location: " The subgroup of patients in Cohort A patients must additionally meet the following criteria to be eligible to start treatment with fitusiran directly after the screening period: 1) Hemophilia B with inhibitory antibody to Factor IX as defined above; 2) Not responding adequately to BPA treatment (historical ABR ≥20) prior to enrollment; and 3) in the opinion of the Investigator, with approval of Sponsor Medical Monitor, 6-month BPA prophylaxis period should be omitted." | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |
| Synopsis: Reference Therapy, Dose and Mode of Administration | Following sentence added at appropriate location: "The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate into this BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period." | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |
| Synopsis: Duration of Treatment | Following sentences "The estimated total time on study, inclusive of Screening, for each patient is up to 15 months for patients who enroll in the extension study. The estimated total time on study may be up to 21 months in 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." changed to "The estimated total time on study, inclusive of Screening, for each patient is up to 15 months for patients who enroll in the extension study except for patients in the subgroup of Cohort A, which is up to 9 months. The estimated total time on study may be up to 21 months (up to 15 months in patients in the subgroup of Cohort A) in 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." | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis: Statistical Methods | Following sentence "The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not be part of the efficacy analysis set; however their efficacy data will be presented separately." is added in first paragraph.<br>Following sentence "The p-value should be interpreted with caution." is added in second paragraph before "In addition, as a contrast Bayesian analyses will be performed to summarize the point estimates of the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty."<br>Following sentence: "Change in Haem-A-QOL physical health score and total score in the factor/BPA prophylaxis period and fitusiran treatment period will be summarized descriptively." is changed to "Change in Haem-A-QOL physical health score and total score in the factor/BPA prophylaxis period and fitusiran treatment period will be summarized descriptively. A mixed model for repeated measures analysis may be performed as deemed appropriate. The annualized weight-adjusted consumption of factor/BPA injections will be summarized using descriptive statistics." | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |
| Table 1: Schedule of Assessments | The following tests:<br>"Exploratory biomarkers [m, r]"<br>"Urine Collection for Biomarkers [m]" are now:<br>"Exploratory biomarkers [m, r] (optional)"<br>"Urine Collection for Biomarkers [m] (optional)" | These samples are now optional. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 1: Schedule of Assessments | Following sentence added in footnote "a": "The subgroup Cohort A patients who are not responding adequately to BPA prophylaxis treatment will not participate in the BPA prophylaxis period and will directly start the fitusiran treatment period after the screening period. For these patients, the screening period will be from Day -60 to Day 0 and assessments during the BPA prophylaxis period are not applicable with the exception of the exploratory DNA sample." | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |
| Table 1: Schedule of Assessments | Following sentence removed at the end of footnote "a": "For the Republic of Ireland specific requirements, see Appendix 11.5.1.1" | Since the Republic of Ireland amendment is extended to the global protocol, it is no more specific to the Republic of Ireland. |
| Table 1: Schedule of Assessments | Following sentence added at the end of footnote "a, b, n & v": "For the United States specific requirements, see Appendix 11.5.1.1" | This is the United States specific protocol amendment to limit the enrollment to patients with inhibitory antibodies to Factor VIII or Factor IX. |
| Table 1: Schedule of Assessments | Following sentence in footnote n "The pre-dose TG draw should be a volume of 15 ml."' is changed to "The pre-dose TG draw should be a volume of 13.5 mL." | Typo correction. |
| Table 1: Schedule of Assessments | Footnote i "Height will be recorded at Screening only. Weight will be recorded at all other visits (Section 7.5.2)." is changed to "Height will be recorded only at Screening for patients >18 years old. Height for patients <18 years old and weight for all patients will be recorded at all checked visits (Section 7.5.2)." | Typo correction. |
| Table 2: Bleeding Episode Assessments – Unscheduled Visit | The following row is deleted<br>"Exploratory Coagulation" | These samples are no longer collected. |
| Table 2: Bleeding Episode Assessments – Unscheduled Visit | Footnote b is removed | These samples are no longer collected. |
| Table 2: Bleeding Episode Assessments – Unscheduled Visit | Following sentence added under the Table: "For the United States specific requirements, see Appendix 11.5.1.1" | This is the United States specific protocol amendment to limit the enrollment to patients with inhibitory antibodies to Factor VIII or Factor IX. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3 Study Design Rationale | Following sentence "Secondary endpoints characterize annualized spontaneous and joint bleeding rates, change in Haem A QoL physical health score and total score in patients ≥17 years of age, ABR in the onset period, and overall safety profile." Changed to "Secondary endpoints characterize annualized spontaneous and joint bleeding rates, change in Haem A QoL physical health score and total score in patients ≥17 years of age, ABR in the onset period, overall safety profile and the consumption of factor/BPA." | A secondary objective and endpoint are included to further assess fitusiran efficacy. |
| Section 2.2. Secondary Objectives | "To characterize the annualized weight-adjusted consumption of factor/BPA while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis" is added as a secondary objective | A secondary objective and endpoint are included to further assess fitusiran efficacy. |
| Section 3.2. Secondary Endpoints | "Annualized weight-adjusted consumption of factor/BPA" is added as a secondary endpoint | A secondary objective and endpoint are included to further assess fitusiran efficacy. |
| Section 7.3.4. Exploratory Analyses | Following sentence "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." is changed to "Except where prohibited by local or national regulations, in consented patients (since optional), 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." | These samples are now optional. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 7.3.4. Exploratory Analyses | Following sentence "In addition, where permitted in consented patients, serum samples may be used for analysis of circulating RNA, including the assessment of cleaved antithrombin 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." is changed to "In addition, where permitted in consented patients (since optional), serum samples may be used for analysis of circulating RNA, including the assessment of cleaved antithrombin 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." | Clarification that these tests are optional is made. |
| Section 8.2.5.2. Secondary Endpoints | Following sentence is added "The secondary endpoint of annualized weight-adjusted consumption of factor/BPA injections will be summarized using descriptive statistics" | A secondary objective and endpoint are included to further assess fitusiran efficacy. |
| Section 1.3 Study Design Rationale<br>Section 4.1 Summary of Study Design<br>Section 4.2 Duration of Treatment<br>Section 4.3 Number of Patients<br>Section 5.1 Inclusion Criteria (criterion 4)<br>Section 5.3 Removal from Therapy or Assessment<br>Section 6.3.1.1 Routine Use of Factor or Bypassing Agent Prophylaxis in the Factor or Bypassing Agent Prophylaxis Period<br>Section 6.3.2.1 Bleeding Episode Management Recommendations for Patients during the Factor or Bypassing Agent Prophylaxis Period (Patients Not Receiving Fitusiran)<br>Table 5: Bleed Management Dosing Guidelines by Specific Product<br>Section 6.9 Treatment Compliance<br>Section 7.2.1 Electronic diary<br>Section 7.3.3 Coagulation/Thrombin Generation Response Assessment in Factor or Bypassing Agent Prophylaxis Period<br>Section 7.5.5.1 Additional Laboratory Assessments | Following sentence removed: "For the Republic of Ireland specific requirements, see Appendix 11.5.1.2" | Since the Republic of Ireland amendment is extended to the global protocol, it is no more specific to the Republic of Ireland. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3 Study Design Rationale<br>Section 1.5 Benefit-Risk Assessment<br>Section 2 Objectives<br>Section 3 Endpoints<br>Section 4.1 Summary of Study Design<br>Figure 1: Study Design<br>Figure 2: Study Design (for Subgroup of Cohort A Patients Enrolling Directly In to the Fitusiran Treatment Period)<br>Section 4.3 Number of Patients<br>Section 5.1 Inclusion Criteria<br>Section 5.2. Exclusion Criteria<br>Section 5.3 Removal from Therapy or Assessment<br>Section 6.3.1<br>Section 6.3.1.1 Routine Use of Factor or Bypassing Agent Prophylaxis in the Factor or Bypassing Agent Prophylaxis Period<br>Table 4<br>Section 6.3.1.2. Management of Factor or Bypassing Agent Prophylaxis During the Transition to the Fitusiran Treatment Period<br>Section 6.3.2 (subsections 6.3.2.1, 6.3.2.2, 6.3.2.3) Management of Bleeding Episodes<br>Table 5: Bleed Management Dosing Guidelines by Specific Product<br>Section 6.5.Monitoring and Management of Thrombotic Events<br>Section 6.9 Treatment Compliance<br>Section 7.1. Screening/Baseline Assessments<br>Section 7.2. Efficacy Assessments<br>Section 7.2.1 Electronic diary<br>Section 7.3.3 Coagulation/Thrombin Generation Response Assessment in Factor or Bypassing Agent Prophylaxis Period<br>Section 7.5.5.1 Additional Laboratory Assessments<br>Section 8.1 Determination of sample size<br>Section 8.2.5.1 Primary Endpoint | Following sentence added at appropriate location of these sections: “For the United States specific requirements, see Appendix 11.5.1.2” | This is the United States specific protocol amendment to limit the enrollment to patients with inhibitory antibodies to Factor VIII or Factor IX. |
| Section 3.2: Secondary Endpoints | Secondary endpoint “Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period” completed to “Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period” | Correction of a discrepancy with the corresponding study objective. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.3.2.2. Bleeding Episode Management Recommendations for Patients during the Fitusiran Treatment Period<br>Table 5: Bleed Management Dosing Guidelines by Specific Product<br>Section 6.5. Monitoring and Management of Thrombotic Events<br>Section 6.8 Contraceptive Requirements | Following sentence added at appropriate location of these sections: "For the Japan specific requirements, see Appendix 11.5.2" | This is the Japan specific protocol amendment to include previous PMDA recommendations previously managed as protocol addendum administrative changes. |
| Section 8.2.1 Populations to be Analyzed | The whole section is changed to:<br>The populations (analysis sets) are defined as follows:<br>Safety Analysis Set: All patients who enrolled and then received any dose of fitusiran.<br>Efficacy Analysis Set (EAS): All patients in the safety analysis set who received both factor or BPA prophylaxis and any dose of fitusiran (Addressed in more details in SAP).<br>Per-protocol Analysis Set (PPS): All patients In the EAS who had no major protocol deviations. Major deviations will be specified in the SAP.<br>PK Analysis Set: All patients who received any dose of fitusiran and have at least 1 post dose blood sample for PK parameters and have evaluable PK data.<br>The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment will be included in the safety analysis set. They will not be part of the efficacy analysis set. However, their efficacy data will be presented separately. | Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment. |
| Appendix 11.5 | Republic of Ireland-specific requirements have been removed. | Since the Republic of Ireland amendment is extended to the global protocol, it is no more specific to the Republic of Ireland. |
| Appendix 11.5 | United States specific requirements have been added. The changes are identified in the Appendix 11.5.1. | This is the United States specific protocol amendment to limit the enrollment to patients with inhibitory antibodies to Factor VIII or Factor IX. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Appendix 11.5 | Japan specific requirements have been added. The changes are identified in the Appendix 11.5.2. | This is the Japan specific protocol amendment to include previous PMDA recommendations previously managed as protocol addendum administrative changes |
| Appendix 11.6.3 | Newly added appendix. Texts from the "Document History" page have been moved to this appendix. | Due to change in the amendment number, overall rationale and summary of changes of protocol amendment 03 have been moved to Appendix 11.6.3. |

### 11.7.5 Amended Protocol 05

**AMENDMENT 05 (25 November 2020)**

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**OVERALL RATIONALE FOR THE AMENDMENT**

- The main purpose of this amendment is to introduce a risk mitigation strategy for vascular thrombotic events in patients exposed to fitusiran. This strategy aims to decrease the level of antithrombin reduction via a change in the fitusiran dosing regimen. A Schedule of Assessments was added to accommodate the new dose regimen and to ensure optimal monitoring during the transition.
- Cholecystitis and symptomatic cholelithiasis are newly identified risk of fitusiran. As such, cholecystitis and cholelithiasis have been added to the protocol as adverse events of special interest (AESIs).
- The amendment also includes the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic. The guidance provides instruction on how to ensure continued dosing, monitor patients and perform assessments remotely when study patients are unable to travel to the site.
- Other minor editorial changes have been made to improve the clarity and readability of the protocol.

**Protocol amendment summary of changes table**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis: Study design<br>Section 4.1: Summary of study design<br>Section 11.6.1.1: Protocol synopsis | Text changed from "…receive their first dose of 80 mg fitusiran" to "…receive their first dose of fitusiran" | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Synopsis: Study design<br>Section 4.1: Summary of study design<br>Section 11.6.1.1: Protocol synopsis | Text changed from "…receive 80 mg fitusiran as a once monthly prophylaxis" to "…receive fitusiran as prophylaxis" | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Synopsis: Study design<br>Section 4.1: Summary of study design<br>Section 11.6.1.1: Protocol synopsis | Text changed from "…with fitusiran for a total of 7 months and will receive 7 SC injections of fitusiran." to "…with fitusiran for a total of 7 months." | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Synopsis: Number of planned patients<br>Section 4.3: Number of patients<br>Section 11.6.1.1: Protocol synopsis | Text updated from "Approximately 70 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 40 patients without inhibitors (Cohort B)." to "Approximately 80 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 50 patients without inhibitors (Cohort B)." | Study expanded to include patients to mitigate for the over enrollment of the non-inhibitor cohort as there were already 79 patients enrolled at the time of this amendment. |
| Synopsis: Investigational product, dose and mode of administration<br>Section 6.2.2: Dose and administration | Text changed from "Patients will receive open-label fitusiran 80 mg as an SC injection once monthly injection" to "Patients will receive open-label fitusiran as an SC injection". | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Table 1: Schedule of assessments | Table updated with 12-Lead ECG not to be checked at Month 5. | ECG is expected to be performed pre and post dose of fitusiran, so deleted with the change of dose frequency. |
| Table 1: Schedule of assessments | Table updated with Antidrug Antibodies samples to be collected at Day 1, Month 2, Month 4, Month 6, and Month 7. | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Table 1: Schedule of assessments | Table updated with Plasma PK samples to be collected at Day 1, Month 2, Month 4, Month 6, and clarified "Plasma PK (East Asian patients only)". | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Table 1: Schedule of assessments | Table updated with Fitusiran Administration Q2M schedule to be injected at Day 1, Month 2, Month 4, and Month 6. | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 1: Schedule of assessments | Text changed from "Review with patient at each visit and contact every 2 weeks between visits" to "Review with patient at each visit and contact every 2 weeks (±4 days) between visits" for Bleed Management Review and Bleeding Episodes/eDiary. | Window added for flexibility. |
| Table 1: Schedule of assessments | Table updated with COVID-19 Testing to be done at any time during the study. | To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic. |
| Table 1: Schedule of assessments | Note "AT and factor results will be provided at screening for confirmation of eligibility. AT results will be provided at AT follow-up visits for monitoring." from previous amended protocol 04 removed. | AT results and Factor results during the study will be provided |
| Table 1: Schedule of assessments | Foot note "j" changed from: "…On Day 1 and Month 5, …" to "…On Day 1, …" | ECG is expected to be performed pre and post dose of fitusiran, so deleted with the change of dose frequency. |
| Table 1: Schedule of assessments | Foot note "n", the flowing sentence was removed: "The pre-dose TG draw should be a volume of 13.5 mL." | Usually volume is not mentioned in the protocols but rather in lab manuals only. |
| Table 1: Schedule of assessments | Foot note "o" in previous amended protocol 4 "Only for patients who do not enroll in the open-label extension study" removed | Both "Nijmegen-Modified Bethesda Assay (Inhibitor Status)" and "antidrug antibody test" are required for patients who roll over to the OLE study. |
| Table 1: Schedule of assessments | Foot note "p" changed from "East Asian patients at East Asian sites, blood samples for PK analysis will be collected at the time points listed in (which includes all those time points listed in), and pooled urine samples will be collected for PK analysis at the time points listed in …" to "Pooled urine samples will be collected for PK analysis at the time points listed in..." | Draws will now be the same for all patients whether East Asian or not. |
| Table 1: Schedule of assessments | Foot note "r" changed from "…in patients undergoing operative procedures while on study" to "…in patients undergoing major operative procedures while on study drug". | For clarity. |
| Table 1: Schedule of assessments | New foot note "x" added: "All study patients that are consenting to this procedure are requested to undergo testing for SARS-CoV-2 (virus responsible for COVID-19), which should include both RT-PCR and antibody testing. These tests should be performed as early as possible during the study. | To clarify COVID-19 test. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Alternatively, historical test results may be provided under certain circumstances as defined by the Sponsor." | |
| List of abbreviations<br>Section 6.2.6: Accountability | Abbreviation for DTP changed from "duties and taxes paid" to "Direct-to-Patient". | Typo. |
| Section 1.1: Disease overview | Text updated from "Hemophilia A is found in approximately 1 in 5000 males whereas hemophilia B is five times less common and seen in approximately 1 in 25,000 males" to "Hemophilia A is found in approximately 1 in 4000 males whereas hemophilia B is five times less common and seen in approximately 1 in 20,000 males". | Reference updated. |
| Section 1.1: Disease overview | Text updated from "In 20% to 33% of patients with hemophilia A, inhibitory antibodies form to FVIII; in hemophilia B, 1% to 6% of patients develop inhibitory antibodies to FIX" to "Development of inhibitors to infused factor occurs mainly in severe hemophilia, and more frequently in hemophilia A (up to 39% of patients) (5,6) than in hemophilia B (1% to 3.5% of patients) (7,8) with the greatest risk of development in the early exposure days.". | Reference updated. |
| Section 1.1: Disease overview | Text changed from "A fixed-dose subcutaneous therapy…" to "A subcutaneous therapy…". | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Section 1.2: Fitusiran (SAR439774) | Text changed from ", the subcutaneous (SC) administration required is notably less frequent (once monthly) than…" to ", the subcutaneous (SC) administration required is notably less frequent than…". | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Section 1.2.2: Summary of clinical data section | Simplified. | Refer to the IB for current updates. |
| Section 1.2.2.1: Summary of efficacy | Paragraphs 1 to 3 from previous amended protocol 04 removed, the following paragraph added: "Phase 1/2 clinical trials, monthly dosing with fitusiran in patients with hemophilia A and B, with or without inhibitors resulted in sustained antithrombin lowering and improved hemostasis as measured by reductions in patients' annualized bleeding rate (ABR) (9, 10).". | Refer to the IB for current updates. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.2.2.2: Summary of safety | Paragraphs 1 to 6 from previous amended protocol 04 removed, the following paragraph added: "Events of serious vascular thrombosis, liver transaminase abnormalities, cholecystitis, and symptomatic cholelithiasis have been reported in the clinical development program and are considered identified risks of fitusiran. In addition, serious hypersensitivity reactions, including injection site reactions, are considered a potential risk of fitusiran. One death has been reported in a patient with cerebral venous thrombosis (CVST) in ALN-AT3SC-002. In response to this event, the bleed management guidelines were revised in December 2017. " | Refer to the IB for current updates. |
| Section 1.4: Dose rationale | Dose rationale text updated, dosing regimen simulation added, Table 3 added. | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Section 1.5: Benefit-risk assessment<br>Section 11.6.1.2: Protocol body | Benefit-risk assessment text updated. | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Section 4.4: Summary of study design | Text changed from "All patients will be assigned to the same treatment sequence in this open-label study." to "All patients will be assigned to the same treatment sequence (prophylaxis period followed by fitusiran period) in this open-label study.". | For clarity. |
| Section 5.3.1: Discontinuation of study drug | New bullet added "More than 1 AT measurements <15% if at a dose of 50 mg Q2M". | To align with instructions for AT-driven fitusiran regimen modification |
| Section 5.3.3: Criteria for temporarily delaying enrollment or administrations of study intervention | New section "Criteria for temporarily delaying enrollment or administrations of study intervention" added. | To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic. |
| Section 6.1: Treatments administered | The following paragraphs added: "The IMP may be supplied at the site or from the Investigator/site/Sponsor to the patient via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the patient.<br>For a regional or national emergency declared by a governmental agency that | To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 11.8. | |
| Section 6.2.3: Dose modifications | The following sentence added: "Instructions for AT-driven fitusiran regimen modification are provided in Section 6.2.3.1." | To align with the new fitusiran dosing regimen. |
| Section 6.2.3.2: Antithrombin level criteria for a dose adjustment | New section added. | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Section 6.2.3.3: Temporary discontinuation due to a regional or national emergency | New section added. | To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic. |
| Section 6.5: Monitoring and management of thrombotic events | Monitoring and management of thrombotic events text updated. | Risk mitigation measure for vascular thrombotic events. |
| Section 6.6: Elective and/or emergency surgery | Text changed from "If an urgent need for surgery arises during…" to "If an urgent need for major surgery arises during…".<br>"In patients undergoing surgery during the study, …" changed to "In patients undergoing major surgery during the study, …". | For clarity. |
| Section 7: Study assessment | The following sentence from previous amended protocol 04 removed "Additional information on the collection of study assessments will be detailed in the Study Manual." | It was an error as no study manual provided for this study. |
| Section 7: Study assessment | The following sentence added "For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 11.8." | To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic. |
| Section 7.1: Screening/baseline assessments<br>Section 11.6.1.2: Protocol body | Text changed from "…must be signed by the patient (or legal guardian) before the Screening/Baseline procedures are initiated" to "…must be signed by the patient (or legal guardian) before the Screening procedures are initiated" | For clarity. |
| Section 7.2.1: Electronic diary<br>Section 11.6.1.2: Protocol body | Text changed from "The site will contact the patient at a minimum interval of every 2 weeks per schedule of assessments…" to "The site will contact the patient at a minimum interval of every 2 weeks (+/- 4 days) per schedule of assessments…". | Window added for flexibility |
| Section 7.2.1: Electronic diary | Text changed from "Sponsor or an independent delegate" to "Sponsor". | No independent reviewer of eDiary data |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section11.6.1.2: Protocol body | | |
| Section 7.2.1: Electronic diary<br>Section 11.6.1.2: Protocol body | The following sentence removed "Complete instructions will be provided in the Study Manual." | It was an error as no study manual provided for this study. |
| Section 7.3.1: Antithrombin (AT) activity | Text changed from "Samples will be collected within 4 hours prior to dosing." to "On dosing days, samples will be collected within 4 hours prior to dosing." | For clarity. |
| Section 7.3.1: Antithrombin (AT) activity | Text changed from "Following final fitusiran dose, AT activity level will be monitored" to "Following final fitusiran dose, and in case the patient is not rolled over to the open label extension study, AT activity level will be monitored". | For clarity. |
| Section 7.4: Pharmacokinetic assessments | Text changed from "All plasma concentration data (Table 11) will be summarized and analyzed using a population PK" to "All plasma concentration data (Table 11) will be summarized and analyzed using a population PK approach and noncompartmental analysis, as applicable." | For clarity. |
| Section 7.4: Pharmacokinetic assessments | Text changed from "In addition, plasma PK (Table 11, which includes all time points in Table 10) will be evaluated in East Asian patients 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" to "In addition, there will be pooled urine collection for urine PK analysis also in patients from East Asian sites (defined as patients from sites in China, Japan, South Korea, and Taiwan). This does not apply to patients on the 50 mg Q2M dosing regimen.". | Need to collect any urine data from any patients after dose switch to 50 mg Q2M regimen. |
| Section 7.5: Use of biological samples and data for future research | New section added. | To align with new template mandatory text. |
| Section 7.6.4: Electrocardiogram | Text changed from "Recordings will be archived according to the Study Manual." to "Recordings will be archived at sites." | It was an error as no study manual provided for this study. |
| Section 7.6.6.1: Definitions | ASEI: Cholecystitis and Cholelithiasis added. | To reflect the updates of fitusiran safety profile and to optimize the monitoring process. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 7.6.6.3: Serious adverse events and adverse events of special interest require immediate reporting to Sponsor/Designee | The following sentence removed: "SAEs must be reported using the contact information provided in the Study Manual." | It was an error as no study manual provided for this study. |
| Section 7.7.1: Patient-reported outcomes | Text changed from "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." to "All completed questionnaires or instrument forms for the patient-reported outcome assessments described below will be collected, entered into a database, and archived at study sites." | It was an error as no study manual provided for this study. |
| Section 7.7.2: HJHS | Text changed from "Completed HJHS score forms will be collected and archived according to the Study Manual." to "Completed HJHS score forms will be collected and archived at study sites." | It was an error as no study manual provided for this study. |
| Section 8.1: Determination of sample size | Text changed from "The overall sample size of 70 patients including approximately 30 patients with inhibitor (Cohort A) and approximately 40 patients without inhibitor (Cohort B) was selected" to "The overall sample size of 80 patients including approximately 30 patients with inhibitor (Cohort A) and approximately 50 patients without inhibitor (Cohort B) was selected". | Study expanded to include patients to mitigate for the over enrollment of the non-inhibitor cohort as there were already 79 patients enrolled at the time of this amendment. |
| Section 8.2.1: Populations to be analyzed | COVID-19 Unaffected Set added: All patients who had no major or critical protocol deviations due to COVID-19 at any visit up to the end of study (Month 7). | To define Covid-19 Unaffected Set. |
| Section 8.2.5: Efficacy analyses | The following paragraph added: "To address the potential impact of COVID-19, the efficacy analyses will be repeated on the COVID-19 unaffected set. Additional analyses and methods required to evaluate the impact are detailed in the SAP". | To add the efficacy analyses due to Covid-19 impact to address the potential impact. |
| Section 9.2.1: Data handling | Text changed from "The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents." to | For clarity. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | "The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (including remote access, if possible and authorized).". | |
| Section 9.2.2: Study monitoring | The following paragraph added: "Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents." | To include proactive monitoring details. |
| Section 9.2.2: Study monitoring | Text changed from "…must be retained by the Investigator for 15 years after study completion" to "must be retained by the Investigator for 25 years after study completion". | To align with the updated requirement. |
| List of Reference | Reference list updated. | New references were added |
| Table 11: Pharmacokinetic time points in East Asian patients following fitusiran administration at 50 mg Q2M | Updated. | Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. |
| Table 11 and Table 12 from previous amended protocol 04 | Removed. | Sampling updated. |
| Appendices Section 11.2.2: Perioperative assessments of safety and hemostatic efficacy in patients undergoing operative procedures | Text changed from "In patients undergoing operative procedures during the fitusiran treatment period…" to "In patients undergoing major operative procedures during the fitusiran treatment period…". | For clarity. |
| Appendices Section 11.5: Data protection" | New section added. | To align with new template mandatory text. |
| Appendices Section 11.8 | New section added "Contingency measures for a regional or national emergency that is declared by a governmental agency". | To clarify contingency measures for a regional or national emergency such the COVID-19 pandemic. |
| Throughout | Minor editorial, typo error corrections and document formatting revisions | Minor, therefore, have not been summarized |

## 11.8 CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

### Clinical supplies and dosing

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained) to make clinical supplies available to the participant for the duration of the emergency:

- The Direct-to-Patient (DTP) supply of IMP via Investigator or Sponsor approved courier where allowed by local regulations and agreed upon by the participant.
- Re-initiation of the IMP can only occur once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

### Operational measures

Contingency procedures for continuation of the study in the event of a regional or national emergency declared by a governmental agency are suggested below and in Section 5.3.3, Section 6.1, Section 6.2.3.3, and Section 7. These procedures apply to an emergency that prevents access to the study site, to optimize the safety of the study patients, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data. Home injection with IMP can be performed as per Investigator's judgement. For any patient receiving fitusiran, BPAs, Investigator or designee should contact the patient via regular phone calls at least every two weeks to oversee the tolerability of the drugs, check for AEs, review bleed management including bleeding episodes and eDiary. Depending on the delay of patient on-site visit, Patient Reported Outcomes (PRO) ie, questionnaires) collection may also be considered via remote visits.
- If onsite visits are not feasible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. If a visit cannot be completed in its entirety, at a minimum the site should maintain contact with patients every 2 weeks, to check for AEs, review the bleed management including bleeding episodes and eDiary.

- Use of a local laboratory may be allowed; Hematology, serum chemistry, coagulation, and liver function tests (which are due at certain visits and which cannot be frozen) should be prioritized for local lab testing by the study site for continued safety assessment.

Contingencies implemented due to emergency will be documented.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/administration of study intervention may be temporarily delayed (see also Section 7).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to optimize the safety of patients and those important to preserving the main scientific value of the study.

The patient or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays, treatment extension, use of local labs etc).

Signature Page for VV-CLIN-0254442 v4.0
efc15110-16-1-1-amended-protocol06

| | |
|---|---|
| Approve & eSign | [redacted]<br>Clinical<br>[redacted] |

| | |
|---|---|
| Approve & eSign | [redacted]<br>Clinical<br>[redacted] |