SANOFI GENZYME

CLINICAL STUDY PROTOCOL

ALN-AT3SC-003 (Sanofi Genzyme EFC14768)

Protocol Title:	ATLAS-INH: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, with Inhibitory Antibodies to Factor VIII or IX
Investigational Drug:	Fitusiran (SAR439774 [formerly Alnylam ALN-AT3SC])
EudraCT Number:	2016-001463-36
Protocol Date:	Original protocol, 19 May 2017 Amendment 1, 09 Nov 2017 Amendment 2, 27 Jun 2018
Sponsor:	Genzyme Corporation, 50 Binney Street, Cambridge, MA 02142, USA
Sponsor Contact:	[redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country-specificity if applicable	Date
Amendment 02	NA	27 Jun 2018
Amendment 01	NA	09 Nov 2017
Original Protocol	NA	19 May 2017

AMENDMENT 02 (27 Jun 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 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 (EFC14768) has been added. The Alnylam study drug code ALN-AT3SC has also been updated to the generic drug name fitusiran (SAR439774). 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.

Protocol amendment summary of changes table

Section #	Description of Change	Brief Rationale
Throughout	Sponsor changed from "Alnylam Pharmaceuticals, Inc." to "Genzyme Corporation"	Change of protocol Sponsor
Throughout	Name of product "ALN-AT3SC" changed to "SAR439774 Fitusiran"	Change of protocol Sponsor; name of product updated
Title page	Name of Sponsor contact changed from [redacted] to [redacted]	Change of protocol Sponsor; contact details
Title page	Disclaimer note text changed	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Synopsis	Age of adolescents changed from "≥12 to <18 years of age" to "≥12 to <17 years of age" for HRQOL	For clarity
Protocol synopsis, document header, title page, and Section 1.3 (only at first occurrence)	"Sanofi Genzyme EFC14768" added to the Study number "ALN-AT3SC-003"	Change of protocol Sponsor; Sanofi Genzyme study ID required for administrative purposes on first use
Protocol synopsis and Section 3.2 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 in statistical plan; text aligned with Sanofi Genzyme environment
Table 1 (Footnote 'n'), Section 7.3.1 and Section 7.5.5.2	Sample collection time period for AT activity levels and antidrug antibody levels changed from "1 hour" to "4 hours" prior to dosing on dosing days for patients on the fitusiran arm	Due to logistical and/or operational reasons
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
Throughout	"Study drug" changed to "Investigational medicinal product"	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Protocol synopsis and Section 4.2	Duration of treatment language updated	For clarity
Section 1.3	"ALN-AT3SC-004" changed to "ALN-AT3SC-004 [EFC14769]"	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 6.2.6	"Accountability" section updated with	Change of protocol Sponsor; text aligned with Sanofi

Section #	Description of Change	Brief Rationale
	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, defect in quality of IMP reporting, recall procedure, restriction of use and dispose of IMP etc.)	Genzyme environment
Throughout	"Adverse events of clinical interest" changed to "Adverse events of special interest"	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 7.5.5 (Table 5)	Hepatitis B surface antibody (anti-HBs) deleted	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment, and scientific rationale for the change
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, and to provide scientific rationale for inclusion of IARs to AESI
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 Sponsor/Designee" to "Serious Adverse Events and Adverse Events of Special Interest Require Immediate Reporting to Sponsor/Designee"	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 7.5.6.7	Overdose reporting section 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 "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."	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 8.2.5.1	Text related to "Sensitivity Analysis" is added	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
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	Change of protocol Sponsor; text aligned with Sanofi

Section #	Description of Change	Brief Rationale
	updated to provide additional process details/clarity	Genzyme environment
Section 9.1.2	Ethical Review language updated for clarity	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
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

NAMES AND ADRESSES OF:

MONITORING TEAM'S REPRESENTATIVE

Name:	
Address:	
Tel:	
Fax:	
E-mail	

SPONSOR

Name:	Genzyme Corporation
Address:	50 Binney Street Cambridge, MA 02142, USA

PROTOCOL SYNOPSIS

Protocol Title

ATLAS-INH: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, with Inhibitory Antibodies to Factor VIII or IX

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 centers

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

Objectives

Primary

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

Secondary

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

Exploratory

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

total weight-adjusted consumption of BPAs

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

Endpoints

Primary

- Annualized Bleeding Rate (ABR) in the efficacy period

Secondary

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

Exploratory

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

Safety

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

Study Design

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

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

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

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

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

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

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

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

Number of Planned Patients

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

Diagnosis and Main Eligibility Criteria

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

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

Investigational Product, Dose and Mode of Administration

Fitusiran is an SC administered N-acetylgalactosamine (GalNAc)-conjugated siRNA targeting liver-expressed messenger RNA (mRNA) for AT.

Patients randomized to the fitusiran treatment arm will receive open label fitusiran 80 mg as an SC injection once monthly, for a total of 9 months; dosing will begin on Day 1 of the treatment period.

Reference Therapy, Dose and Mode of Administration

Patients in on-demand arm will receive on-demand BPA therapy per Investigator discretion to treat bleeding episodes from Day 1 through end of study. The protocol will recommend guidance for patients in the fitusiran treatment arm for treatment of breakthrough bleeding episodes during the fitusiran efficacy period.

Duration of Treatment

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

Statistical Methods

Sample Size Calculation

Assuming a mean ABR of 18 with standard deviation (SD) = 14 in the on-demand arm (patients randomized to receive only BPAs) and a mean ABR of no more than 4 with SD = 6 in the fitusiran treatment arm (patients randomized to receive fitusiran) in either the efficacy period or the treatment period, with a sample size of 14 evaluable patients in the on-demand arm and approximately 28 evaluable patients in the fitusiran treatment arm, it is projected that the study will have greater than 90% power for testing treatment difference in mean ABRs. This power estimation was based on negative binomial regression model with a 2-sided Type I error rate of 0.05. The planned sample size is 54 randomized patients assuming a 20% drop-out rate.

Analyses

The primary analysis will be performed on the intent-to-treat (ITT) analysis set which includes all randomized patients. The primary endpoint will be based on the bleeding episodes occurring in the efficacy period (Day 29 to Day 246) including the data collected after discontinuation of investigational medicinal product (IMP). To avoid confounding the treatment effect, bleeding data during and after major surgery, AT administration, major trauma, or after initiation of prophylaxis treatment with BPA will be excluded from the primary analysis.

The number of bleeding episodes will be analyzed using a negative binomial model with fixed effects of treatment arm and the number of bleeding episodes in the 6 months prior to study entry ($\leq$10 vs >10). 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 the bleeding rate on fitusiran treatment arm relative to the bleeding rate on the on-demand arm and its 95% confidence interval will be presented. Sensitivity analyses will be performed to evaluate the impact of missing data under different missing data mechanisms and details will be specified in the statistical analysis plan.

The bleeding episodes in the treatment period (Day 1 to Day 246), spontaneous bleeding episodes in the efficacy period, joint bleeding episodes in the efficacy period, and the bleeding episodes in the

onset period will be analyzed and compared using the same model as used in the primary analysis. The change from baseline in physical health score and total score of Haem-A-QOL will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects of the treatment arm, baseline Haem-A-QOL physical health score and total score, and the number of bleeding episodes in the 6 months prior to study entry (≤10 vs >10) as covariates.

Familywise error rate will be strongly controlled for the primary endpoint and the selected secondary endpoints using a fixed sequence testing procedure.

Safety results will be summarized descriptively.

Table 1: Schedule of Assessments

Study Visit (Month)		Treatment Period												AT F/U[b,c]
		Onset Period		Efficacy Period										
		Baseline		Month 1		Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	EOT Month 8	EOS/ ET[a,b] Month 9	
Study Day (±Visit Window)	-60 to -1	Day 1	15 ±3	29 ±7	43 ±3	57 ±7	85 ±7	113 ±7	141 ±7	169 ±7	197±7	225±7	253 ±7	281 ±7
Informed Consent/Assent	X													
Medical History[d]	X													
Demographics	X													
Inclusion/Exclusion Criteria	X													
Randomization[e]		X												
eDiary Training[f]	X													
Physical Examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Height[h]	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
12-Lead ECG[i]	X	X									X		X	
FibroScan OR FibroTest/APRI[j]	X													
TG Level[k,l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nijmegen-Modified Bethesda Assay (Inhibitor Status)	X											X	X[m]	
AT Activity Level[k, l, n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII / FIX Levels[k]	X													
Thrombophilia Screening	X													

Table 1: Schedule of Assessments

Study Visit (Month)		Treatment Period												AT F/U[b,c]
		Onset Period		Efficacy Period										
		Baseline		Month 1		Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	EOT	EOS/ ET[a,b]	
												Month 8	Month 9	
Study Day (±Visit Window)	**-60 to -1**	**Day 1**	**15 ±3**	**29 ±7**	**43 ±3**	**57 ±7**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197±7**	**225±7**	**253 ±7**	**281 ±7**
Serum Chemistry[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Function Tests[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Drug Antibodies[k,n, q]	X	X		X			X					X	X[m]	
Hematology[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatic Tests[p]	X													
Exploratory Biomarkers[k]		X					X						X	
Exploratory Circulating RNA (Optional)[k]		X					X						X	
Exploratory DNA Sample (Optional) [k]		X												
Plasma PK[k, r]		X		X			X				X	X		
Urinalysis	X	X											X	
Urine Collection for Biomarkers[k]		X					X						X	
HJHS[s]		X											X[s]	
Patient Resource Use[s]		X											X[s]	
EQ-5D[s]		X											X[s]	
Haem-A-QOL / Haemo-QOL[s]		X											X[s]	
HAL / pedHAL[s]		X											X[s]	

Table 1: Schedule of Assessments

Study Visit (Month)		Treatment Period												AT F/U[b,c]
		Onset Period		Efficacy Period										
		Baseline		Month 1		Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	EOT Month 8	EOS/ ET[a,b] Month 9	
Study Day (±Visit Window)	-60 to -1	Day 1	15 ±3	29 ±7	43 ±3	57 ±7	85 ±7	113 ±7	141 ±7	169 ±7	197±7	225±7	253 ±7	281 ±7
TSQM-9[s]		X											X[s]	
Fitusiran Administration (Fitusiran arm only)		X		X		X	X	X	X	X	X	X		
Patient Education Module Training		X												
Bleed Management Review[t]		Review with patient at each visit and contact every 2 weeks between visits												
Bleeding Episodes/eDiary[u]		Review with patient at each visit and contact every 2 weeks between visits												
Perioperative Assessment[v]		Continuous												
Adverse Events[w]		Continuous												
Concomitant Medications[x]		Continuous												

Abbreviations: AEs = adverse events; AT = antithrombin; 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; Haem-A-QOL = Hemophilia Quality of Life Questionnaire for Adults; Haemo-QOL = Hemophilia Quality of Life Questionnaire for children and adolescents; HAL = Hemophilia Activities List; HJHS = Hemophilia Joint Health Score; IMP = investigational medicinal product; Min = minute; pedHAL = pediatric HAL; PK = pharmacokinetics; 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 baseline do not need to be repeated at the Baseline visit.
- Rescreening of patients is permitted with consultation of the study Medical Monitor.
- Laboratory parameters are described in Section 7.5.5 and listed in Table 5.
- As clinical research parameters, TG, D-dimer, and all other non-safety laboratory parameter results will not be communicated to sites. 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.
- 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] Not required at Early Termination Visit for patients who complete assessment at EOT Visit and subsequently Early Terminate.
[b] Patients in the fitusiran treatment arm who discontinue IMP dosing for any reason and agree to complete the remaining assessments through the EOS/ET visit and AT follow-up and may receive treatment consistent with local standard practice for their disease per Investigator judgment, once AT levels return to ~60% (per the central laboratory) or per Investigator discretion in consultation with the study Medical Monitor. For patients who withdraw from the study early and do not consent to complete remaining assessments through the EOS/ET visit and AT follow-up visits, every effort should be made to conduct the assessments performed at the EOS/ET visit.
[c] Patients in the fitusiran treatment arm 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.
[d] The complete medical history/disease history (ie, including bleeding episode and treatment history over the prior 6 months) to be recorded at Screening.
[e] Randomization may occur within 3 days prior to Day 1.
[f] eDiary training will be completed at the Clinic at Screening (see Section 7.2.1).
[g] A full physical exam will be performed at Screening only; a directed physical exam will be performed at all other visits (see Section 7.5.3).
[h] Height will be recorded at Screening only. Weight will be recorded at all other visits (see Section 7.5.2).
[I] 12-lead ECGs will be performed in triplicate. For patients on Fitusiran: On Day 1 and Month 7, 12-lead ECG will be performed predose and 4 hours (±30 min) postdose (see Section 7.5.4). The Month 9 12-lead ECGs will be performed only in those patients who are performing the ET visit and may be performed in singlicate. For patients in the on-demand arm: On Day 1 and Month 7, two ECG measurements should be performed approximately 4 hours (±30 min) apart.
[j] Hepatitis C virus antibody positive patients only. FibroScan where available, otherwise FibroTest and APRI.
[k] 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.
[l] In addition, AT and TG levels will be performed in East Asian patients at East Asian sites (defined as patients from sites in China, Japan, South Korea, and Taiwan) on Day 2 and Day 8; see Table 8.
[m] Only for patients who do not enroll in the open-label extension study.
[n] For patients on the fitusiran arm, samples will be collected within 4 hours prior to dosing on dosing days.
[o] Serum chemistry and hematology laboratory parameters will be collected as listed in Table 5.
[p] Liver function tests (LFTs) and hepatic tests are listed in Table 5. 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 6. LFT results will be obtained prior to receiving monthly fitusiran dosing.
[q] All patients will be tested for antibodies to fitusiran at the Screening visit. After randomization, testing for antibodies to fitusiran will be performed in the fitusiran treatment arm only.
[r] Blood samples for PK analysis will be collected at the time points listed in Table 7 in all fitusiran arm patients. In East Asian patients in the fitusiran arm at East Asian sites, blood samples for PK analysis will be collected at the time points listed in Table 8 (which includes all those time points listed in Table 7), and pooled urine samples will be collected for PK analysis at the time points listed in Table 9.
[s] Must be completed at the clinic. Will be collected at EOS visit; not collected at ET visit.
[t] 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.
[u] It is strongly preferred that 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.
[v] Perioperative assessment safety and hemostatic efficacy only in patients undergoing operative procedures while on study (see Table 10).
[w] 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)
[x] In addition to recording concomitant medications, documented history of prior medications will be collected during Screening.

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 (If FVIII/FIX products given)	X	X	X
TG	X	X	X
Coagulation	X	X	X
Hematology	X	X	X
Exploratory Coagulation[b]	X		X
Optional Imaging[c]	X		

Abbreviations: AT=antithrombin; BPAs=bypassing agents; FVIII=factor VIII; FIX=factor IX; TG=thrombin generation

[a] See Section 7.5.3 for assessments to be performed during a directed physical examination.

[b] 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.

[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
ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
anti-HCV Ab	Anti-hepatitis C antibody
aPCC	Activated prothrombin complex concentrates
AST	Aspartate aminotransferase
AT	Antithrombin
AUC	Area under the concentration-time curve
BPA	Bypassing agent
BU	Bethesda units
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulation
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CVST	Cerebral venous sinus thrombosis
CYP P450	Cytochrome P450
DMC	Data monitoring committee
DTP	Duties and taxes paid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EQ-5D	EuroQol- 5 dimension

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

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

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 5000 males whereas hemophilia B is five times less common and seen in approximately 1 in 25,000 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.[1]

The disease phenotype presents similarly in hemophilia A and B.[2] 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 (AT), 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 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.[3] Therefore, suppression of AT production is being investigated as a potential hemophilia treatment.

Hemophilia patients who develop inhibitory antibodies to FVIII or FIX represent a distinct subset of the population; these patients typically experience more difficult-to-treat bleeding episodes, leading to increased morbidity and increased mortality.[4] 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.[5] These "inhibitor" patients, may be eligible for immune tolerance therapy, however in most cases bleeding episodes require hemostatic intervention with intravenously administered bypassing agents (BPAs), either as prophylaxis or as on-demand episodic treatment of bleeding episodes, ie, recombinant factor VIIa (rVIIa), or activated prothrombin complex concentrates (aPCC).

A fixed-dose 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 N-acetylgalactosamine (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 (once monthly) 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 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 Cmax 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

Overview Status of Completed and Ongoing Clinical Studies of Fitusiran

Study ALN-AT3SC-001 was a Phase 1 study investigating the safety, tolerability and pharmacokinetics of subcutaneously administered fitusiran in adult male healthy volunteers and

hemophilia A and B adult male patients with moderate or severe hemophilia. The study was conducted in 4 parts:

- Part A (N=4): randomized, placebo-controlled, single-blind single-ascending dose (SAD) phase in healthy subjects (0.03 mg/kg SC single dose)
- Part B (N=12): open-label, multiple-ascending dose (MAD) phase in patients with moderate to severe hemophilia A or B without inhibitors (0.015 to 0.075 mg/kg SC once weekly)
- Part C (N=18): open-label, exploratory multiple dose (MD) phase in patients with moderate to severe hemophilia A or B without inhibitors (0.225 to 1.8 mg/kg or 80 mg fixed dose SC once monthly)
- Part D (N=17): open-label MD phase in patients with moderate to severe hemophilia A or B with inhibitors (50 or 80 mg fixed dose SC once monthly)

Study ALN-AT3SC-001 was completed on 20 July 2017 (last patient last visit).

Study ALN-AT3SC-002 is a Phase 1/2 multicenter, multinational, open-label extension study to evaluate the long-term safety and efficacy of fitusiran in male patients with moderate or severe hemophilia A or B, with or without inhibitors, who previously tolerated dosing in Study ALN-AT3SC-001. Study ALN-AT3SC-002 is currently ongoing. A total of 34 patients who previously participated in Study ALN-AT3SC-001 and received at least 1 dose of SC fitusiran ranging from 0.225 to 1.8 mg/kg or 50 mg or 80 mg fixed doses have enrolled in the extension study. These 34 patients include 19 non-inhibitor patients (14 with hemophilia A and 5 with hemophilia B) and 15 inhibitor patients (13 with hemophilia A and 2 with hemophilia B). Three patients began the extension study on weight-based doses (0.225, 0.9 or 1.8 mg/kg) reflecting their original Phase 1 dose. All patients were transitioned to either 50 mg monthly (N=13) or 80 mg monthly (N=21) after no more than 4 doses. Patients are currently receiving either 50 mg (N=13) or 80 mg (N=21) fixed doses in this extension study, which is ongoing.

For a more complete summary and the most recent available pharmacokinetic, pharmacodynamic, safety and efficacy data see the Investigator's Brochure.

1.2.2.1. Summary of Efficacy

Preliminary efficacy for pooled ALN-AT3SC-001 and ALN-AT3SC-002 data include analysis of annualized bleeding rate (ABR). For the purpose of ABR calculation, fitusiran "Onset Period" and an "Efficacy Period" were defined. The Onset Period was defined as the first 28 days after the first dose of fitusiran, during which the target pharmacodynamic effect is reached. The Efficacy Period, during which bleeds were counted for the purpose of ABR calculation, was defined as starting on Day 29. For patients who did not have an interruption in treatment >56 days between the Phase 1 study (ALN-AT3SC-001) and this Phase 1/2 extension study (ALN-AT3SC-002), bleed data from ALN-AT3SC-001 were included and the Efficacy Period was defined as starting on Day 29 of that study. As of 8 August 2017, 33 of 34 patients enrolled in the extension study met criteria for inclusion in this analysis, with one patient not yet having completed 28 days on study.

Patients entering the extension study all received fitusiran as a once monthly injection. Initial doses ranged from 0.225 mg/kg to 1.8 mg/kg in 3 patients, but all patients were transitioned to either 50 mg (N=13) or 80 mg (N=21) fixed doses after ≤4 doses. No prophylactic use of factor

concentrates or BPAs were allowed after the first dose of fitusiran, with only on-demand use of these agents for the treatment of any breakthrough bleeding events.

The ABR was determined for non-inhibitor and inhibitor patients receiving 50 mg or 80 mg. The prestudy ABR was reported at ALN-AT3SC-001 study entry, prior to beginning treatment with fitusiran. The ABR of patients from combined data from studies ALN-AT3SC-001 and ALN-AT3SC-002 reflects efficacy across hemophilia subtypes in both inhibitor and non-inhibitor patients. In patients on 80 mg monthly, the dose selected for Phase 3 studies, the median ABR during the Efficacy Period (Day 29 to the data cut-off [8 August 2017]) is 1.46 and 0 in non-inhibitor (N=9) and inhibitor (N=11) patients, respectively. The median ABR on 50 mg monthly was 1.57 for non-inhibitor (N=10) and 6.84 for inhibitor (N=3) patients. All of the non-inhibitor patients on prophylactic therapy (N=7) pre-study either maintained low ABR, or demonstrated improved ABR on fitusiran, and the median ABR for this group was 1.7.

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

As of 31 August 2017, 42 male patients with severe or moderate hemophilia A or B, with or without inhibitors, have received fitusiran in clinical studies. Single and multiple doses of fitusiran have been generally well tolerated. Most patients have reported at least 1 AE, the majority of which were assessed as mild or moderate in intensity and unrelated to investigational medicinal product (IMP). The most common AEs reported were injection site reactions, which were all mild and generally transient.

Elevations of liver transaminases occurred in 13 of 42 patients dosed with fitusiran. None of the liver transaminase elevations were associated with elevations of total serum bilirubin >2 × the upper limit of normal (ULN). Except in one patient, these elevations were asymptomatic, and occurred in patients with a documented history of prior HCV infection.

Eleven of 42 patients reported a total of 14 SAEs. Out of these, 3 SAEs (elevated alanine aminotransferase [ALT] and aspartate aminotransferase [AST], seizures, and cerebral venous sinus thrombosis [CVST]) were assessed as possibly related to fitusiran.

Two patients discontinued fitusiran due to AEs (1 due to a non-serious AE of non-cardiac chest pain and another due to SAEs of elevated ALT and AST.

One death has been reported in a patient with CVST in ALN-AT3SC-002, which was considered possibly related to fitusiran. This occurred in a 27-year old patient who had been on study for 15 months. The patient was hospitalized for headache several days after treating hip pain with 31 IU/kg to 46 IU/kg factor VIII. While the patient was initially suspected of having viral meningitis, he was subsequently diagnosed with subarachnoid hemorrhage on the basis of computed tomography (CT) imaging, and treated with full dose Factor VIII concentrate two to three times daily. Over a 14-day hospitalization, the patient's medical condition worsened despite the administration of FVIII concentrate and he died from subsequent cerebral edema. Post mortem review of images by independent neuro-radiologists confirmed that the initiating event was a CVST, and not a subarachnoid hemorrhage. The event is thus categorized as possibly related to fitusiran. No other thromboembolic events have been observed.

No dose-related trend was observed in any of the laboratory, physical exam or EKG results. No consistent dose relationship or clear difference between the 50 mg and 80 mg dose groups was observed with respect to incidence of AEs, SAEs or laboratory tests.

A more detailed summary of 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 Aug 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-INH trial (ALN-AT3SC-003 [Sanofi Genzyme EFC14768]) is a multicenter, multinational, randomized, open-label Phase 3 study designed to demonstrate the efficacy and safety of fitusiran in patients with hemophilia A or B with inhibitory antibodies to FVIII or FIX who are currently treated with on-demand BPAs.

The primary objective is to assess the efficacy of fitusiran on prevention or reduction of bleeding episodes. Secondary objectives are to assess the efficacy of fitusiran on: the number and type of bleeding episodes; HRQOL; and to determine the safety and tolerability of fitusiran.

Blinding is not considered feasible for this study since differences in treatment for each study arm cannot be blinded. The open-label, randomized study design is justified because safety monitoring of theoretical risks such as transaminitis or thrombosis can be objectively verified by laboratory monitoring or objective visualization, eg, ultrasound or CT. Therefore, the safety monitoring of the studied population does not require blinding.

The primary endpoint of the study is ABR in the fitusiran efficacy period (Day 29 to EOS). 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 ABR in the treatment period, annualized spontaneous and joint bleeding rates, change in Hemophilia

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

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

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

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

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

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

1.4. Dose Rationale

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

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

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

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

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

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

1.5. Benefit-Risk Assessment

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

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

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

2. OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objectives

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

2.3. Exploratory Objectives

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

3. ENDPOINTS

3.1. Primary Endpoint

- Annualized Bleeding Rate (ABR) in the efficacy period

3.2. Secondary Endpoints

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

3.3. Exploratory Endpoints

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

3.4. Safety Endpoint

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

4. INVESTIGATIONAL PLAN

4.1. Summary of Study Design

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

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

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

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

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

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

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

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

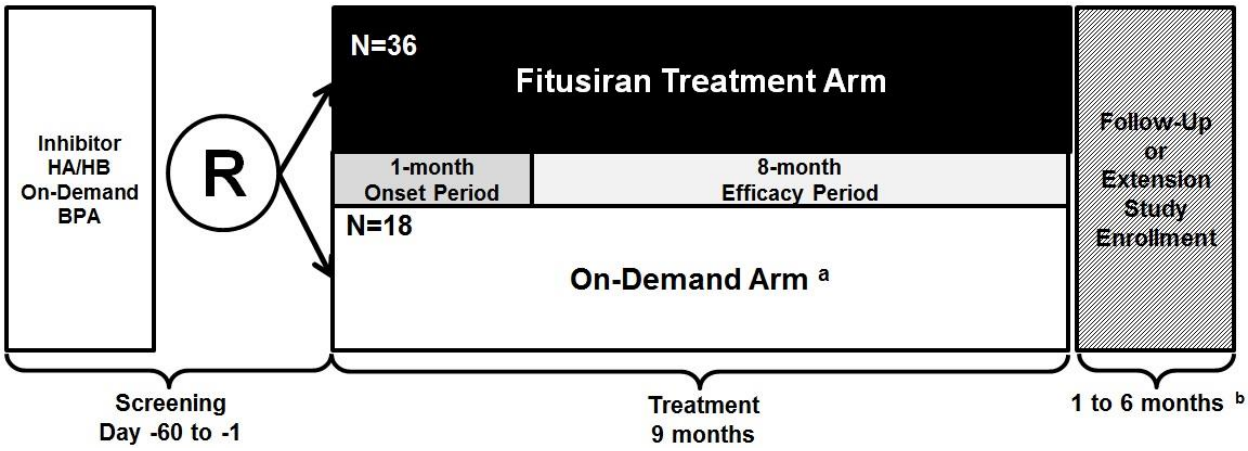
Patients may undergo unplanned or emergency surgery during the study, but must not schedule non-urgent surgery to occur during the study. Perioperative guidance should be followed as specified in Section 6.6.

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

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

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

Figure 1: Study Design



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

4.2. Duration of Treatment

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

4.3. Number of Patients

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

4.4. Method of Assigning Patients to Treatment Groups

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

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

4.5. Blinding

This study is an open-label study so blinding is not applicable; however, performing aggregate summaries of efficacy data by treatment arm 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:

1. Males ≥12 years of age.
2. Severe hemophilia A or B with inhibitors evidenced by:
    a. A central laboratory measurement or documented medical record evidence of FVIII <1% or FIX level ≤2% at Screening.
    b. On-demand use of BPAs to manage 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
3. A minimum of 6 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening.

4. 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:

1. Known co-existing bleeding disorders other than hemophilia A or B, ie, Von Willebrand's disease, additional factor deficiencies, or platelet disorders.
2. Current participation in immune tolerance induction therapy (ITI)
3. Current use of BPAs as regularly administered prophylaxis designed to prevent spontaneous bleeding episodes.
4. AT activity <60% at Screening, as determined by central laboratory measurement.
5. 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
6. 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)
7. Presence of acute hepatitis, ie, hepatitis A, hepatitis E.
8. Presence of acute or chronic hepatitis B infection (IgM anti-HBc antibody positive or HBs Ag positive).
9. Platelet count ≤100,000/μL.
10. Presence of acute infection at Screening.
11. Known to be HIV positive with CD4 count <200 cells/μL.
12. Estimated glomerular filtration rate ≤45 mL/min/1.73 m^2 (using the Modification of Diet in Renal Disease [MDRD] formula).

13. 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 or heterozygous)
14. History of antiphospholipid antibody syndrome.
15. 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.
16. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin that has been successfully treated.
17. 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.
18. At Screening, anticipated need of surgery during the study or planned surgery scheduled to occur during the study.
19. Completion of a surgical procedure within 14 days prior to Screening, or currently receiving additional BPA infusion for postoperative hemostasis.
20. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
21. Inadequate venous access, as determined by the Investigator, to allow the blood draws required by the study protocol.
22. History of intolerance to SC injection(s).
23. 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).
24. Current or prior participation in a gene therapy trial.
25. 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.

Procedures for discontinuation of IMP and/or withdrawal from the study are described in Section 5.3.1 and Section 5.3.2, respectively.

5.3.1. Discontinuation of Investigational Medicinal Product

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 including a life-threatening bleeding episode, eg, any gastrointestinal hemorrhage or intracranial hemorrhage, or life-threatening thromboembolic event
- Requires a prohibited medication.

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 IMP.

In general, patients who discontinue IMP 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 7.5.6. When a patient discontinues IMP dosing, the primary reason must be recorded in the appropriate section of the eCRF. Patients who discontinue IMP 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.

6. TREATMENTS

6.1. Treatments Administered

Investigational medicinal product 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. Investigational medicinal product that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

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 randomized to the fitusiran treatment arm receive open-label 80 mg fitusiran as an SC injection once monthly, for a total of 9 months; dosing will begin on Day 1 of the treatment period.

Investigational medicinal product injection will be administered at the clinic by qualified staff under the supervision of the Investigator or designee. Detailed instructions for IMP administration are found in the Pharmacy Manual.

Investigational medicinal product 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

No fitusiran dose modifications will be allowed.

If a 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 3.
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 3 and Table 6.
   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 3 below:

Table 3: 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
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	  • AT
	• Monitor at least every two weeks (hematology, serum chemistry, LFT, and coagulation per Table 5 and AT)
	• If elevation persists for ≥2 months, must discuss with the study Medical Monitor before continuing dosing

>5× to 8× ULN	• Hold fitusiran dose until recovery to ≤1.5× ULN; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	  • AT
	• Monitor at least weekly (hematology, serum chemistry, LFT, and coagulation per Table 5 and AT) until ALT and/or AST is declining on two consecutive draws, then may decrease monitoring to biweekly
	• 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.

6.2.4. 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 IMP are required.

Investigational medicinal product 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 IMP 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 IMP and additional storage details are provided in the Pharmacy Manual.

6.2.5. Packaging and Labeling

All packaging, labeling, and production of IMP will be in compliance with current Good Manufacturing Practices, or local applicable regulations, where necessary. Investigational medicinal product 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 IMP supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much IMP 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 IMP.

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

Any quality issue noticed with the receipt or use of an 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 7.5.6.8).

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 duties and taxes paid [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 (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, IV infusion of 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 FEIBA and rFVIIa as combination therapy is not recommended.

6.3.1. 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 AEs definitions in Section 7.5.6.1). Bleeding episodes will be recorded in the eDiary. For bleeding episodes in which there was no 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 4 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.

Doses of FVIII and FIX are included for completeness. It is expected that these inhibitor patients will be routinely managed with aPCC or rFVIIa.

6.3.1.1. Bleeding Episode Management Recommendations for Patients in the On-Demand Treatment Arm (Patients Not Receiving Fitusiran)

For patients not receiving fitusiran (on-demand arm), bleeding management therapy with BPAs will be managed based on the local standard practice for treating hemophilia patients with inhibitors, as routinely administered by the physician. 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 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.

6.3.1.2. Bleeding Episode Management Recommendations for Patients in the Fitusiran Treatment Arm

Given the mechanism of action and pharmacodynamics profile of fitusiran, the BPA dose necessary to safely and effectively treat breakthrough bleeding episodes in patients receiving fitusiran (fitusiran treatment arm) 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 BPA regimens for the first 7 days following initiation of fitusiran dosing, with institution of the protocol-specific bleed management guidelines with reduced BPA at Day 8 and beyond (Table 4).

Patients on fitusiran will be provided a written bleed management plan with appropriate dosing of 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, during the treatment period, patients should not use 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: Patients should be instructed to call the site prior to administering factor or BPA. Patients should continue with their standard BPA regimens.

Bleed Management Guidelines Day 8 and Beyond:

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/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 4.
    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 4).

5. Doses should not exceed the protocol maximum recommended dose indicated in Table 4.
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 4
    b. Dosing of factor or BPA at decreased intervals than those recommended in Table 4
    c. Multiple or repeated doses of factor or BPA
7. Antifibrinolytics may not be used in combination with factor or BPA.

Table 4: 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 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 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: Doses of FVIII and FIX are included for completeness. It is expected that these 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.

6.3.1.3. Bleeding Episode Management Following Discontinuation of Fitusiran

Patients who opt to discontinue fitusiran may resume standard on-demand dosing with BPAs 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 full AT recovery (approximately 60% residual activity per the central laboratory), AT replacement should be considered.

6.3.2. 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

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 replacement products or BPAs, there should be a low threshold to evaluate any signs and symptoms consistent with thrombosis, including symptoms consistent with cerebral venous sinus thrombosis (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.[9]

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 patient doses individualized 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).

6.6. Elective and/or Emergency Surgery

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

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

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

Perioperative Treatment Plan

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

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

Fitusiran Treatment During the Perioperative Evaluation Period

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

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

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

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

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

6.7. Management of Sepsis

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

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

6.8. Contraceptive Requirements

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

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

6.9. Treatment Compliance

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

6.10. Alcohol Restrictions

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

7. STUDY ASSESSMENTS

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

7.1. Screening/Baseline Assessments

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

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

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

7.1.1. Patient Education Module

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

7.1.2. Inhibitor Status

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

7.1.3. FibroScan or FibroTest/APRI

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

7.2. Efficacy Assessments

Bleeding Episode Definitions

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

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

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

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

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

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

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

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

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

7.2.1. Electronic Diary

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

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

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

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

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

Complete instructions will be provided in the Study Manual.

7.3. Pharmacodynamic Assessments

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

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

7.3.1. Antithrombin (AT) Activity

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

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

7.3.2. Thrombin Generation

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

7.3.3. Exploratory Analyses

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

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

7.4. Pharmacokinetic Assessments

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

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

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

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

7.5. Safety Assessments

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

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

7.5.1. Vital Signs

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

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

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

Vital signs results will be recorded in the eCRF.

7.5.2. Weight and Height

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

7.5.3. Physical Examination

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

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

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

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

7.5.4. Electrocardiogram

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

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

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

7.5.5. Clinical Laboratory Assessments

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

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

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

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

Table 5: Clinical Laboratory Assessments

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

Table 5: Clinical Laboratory Assessments

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

Note: All assessments will be measured in central laboratory.

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

[a] Will not be communicated to investigational sites.

7.5.5.1. Additional Laboratory Assessments

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

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

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

Table 6: Hepatic Assessments in Patients who Experience LFT Elevations

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

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

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

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

7.5.5.2. Immunogenicity

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

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

7.5.6. Adverse Events

7.5.6.1. Definitions

Adverse Event

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

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

Serious Adverse Event

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

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

Adverse Events of Special Interest

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

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

Adverse Event Severity

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

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

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

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

Relationship of the Adverse Event to Study Treatment

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

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

7.5.6.2. 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 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 IMP 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 7.5.6.1), 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 7.5.6.1. 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.

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

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

The initial report should include at least the following information:

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

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

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

7.5.6.4. Sponsor Safety Reporting to Regulatory Authorities

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

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

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

7.5.6.6. Pregnancy Reporting

There will only be male patients in this study.

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

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

7.5.6.7. Overdose Reporting

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

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

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

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

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

7.6. Other Assessments

7.6.1. Patient-reported Outcomes

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

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

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

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

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

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

7.6.1.2. TSQM-9

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

7.6.1.3. HAL

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

7.6.1.4. EQ-5D-5L

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

7.6.2. Weight-adjusted Consumption of Bypassing Agents

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

7.6.3. HJHS

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

8. STATISTICS

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

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

8.1. Determination of Sample Size

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

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

8.2. Statistical Methodology

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

8.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

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

8.2.2. Examination of Subgroups

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

8.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

8.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized for the ITT Analysis Set and Safety Analysis Set.

8.2.5. Efficacy Analyses

Primary analyses of the primary and secondary endpoints will be based on the ITT Analysis Set.

To control for the familywise error rate in the testing of primary and selected secondary endpoints, a hierarchical testing approach will be used in the following order:

1. ABR in efficacy period (2-sided alpha = 0.05)
2. ABR in treatment period (2-sided alpha = 0.05)
3. Annualized spontaneous bleeding rate in efficacy period (2-sided alpha = 0.05)
4. Annualized joint bleeding rate in efficacy period (2-sided alpha = 0.05)
5. Change in physical health score and total score of Haem-A-QOL in treatment period (2-sided alpha = 0.05)

If testing of any of the endpoints is not statistically significant, testing of subsequent endpoints will stop and the null hypothesis for subsequent tests will not be rejected. The testing of the secondary endpoint ABR in the onset period will not be included in this hierarchical testing procedure.

8.2.5.1. Primary Endpoint

The primary analysis will be performed on the ITT Analysis Set and will include all bleeding episodes occurring in the efficacy period (Day 29 to Day 246) including bleeding episode data collected after discontinuation of IMP. 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 as bleeding episode data of the fitusiran period in the primary analysis. To avoid confounding the treatment effect, bleeding episode data during and after major surgery, AT administration, major trauma, or initiation of prophylaxis treatment with BPAs will be excluded from the primary analysis.

The number of bleeding episodes will be analyzed using a negative binomial model with fixed effects of treatment arm and the number of bleeding episodes in the 6 months prior to study entry ($\leq$10 vs >10). 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 p-value comparing bleeding rates in the 2 treatment arms and the ratio of bleeding rates in the fitusiran treatment arm to the on-demand arm along with its 95% CI will be presented. The estimated mean ABRs in 2 treatment arms 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 encouraged to continue recording bleeding episode data.

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

8.2.5.2. Secondary Endpoints

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

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

8.2.5.3. Exploratory Endpoints

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

8.2.6. Pharmacodynamic Analysis

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

8.2.7. Pharmacokinetic Analysis

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

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

8.2.8. Safety Analyses

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

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

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

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

8.2.9. Other Analysis

Antidrug antibody results will be summarized descriptively.

8.2.10. Interim Analysis

No interim analysis is planned.

9. STUDY ADMINISTRATION

9.1. Ethical and Regulatory Considerations

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

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

9.1.1. Informed Consent Process

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

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

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

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

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

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 printed or 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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 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 publically 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.

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11. APPENDICES

11.1. Pharmacokinetic Assessment Time Points

Table 7 provides a schedule for the collection of blood samples for PK analysis in all fitusiran arm patients.

Table 7: Pharmacokinetic Time Points for All Fitusiran Arm Patients

Study Day	Protocol Time (hh:mm)	PK Blood
Day 1	Predose (within 240 minutes before dosing)[a]	X
	04:00 (±30 min)[a]	X
Day 29 (±7 days)	Predose (within 240 minutes before dosing)[a]	X
Day 85 (±7 days)	Predose (within 240 minutes before dosing)[a]	X
Day 197 (±7 days)	Predose (within 240 minutes before dosing)[a]	X
	04:00 (±30 min)[a]	X
Day 225 (±7 days)	Predose (within 240 minutes before dosing)[a]	X

[a] Time point used in population PK analysis.

Table 8 provides a schedule for the collection of blood samples for PK (fitusiran arm), AT, and thrombin generation analysis in all East Asian patients, at East Asian sites.

Table 8: Pharmacokinetic (Fitusiran Arm), AT, and TG Time Points for East Asian Patients at East Asian Sites

Study Day	Protocol Time (hh:mm)	PK Blood	AT	TG
Day 1	Predose (within 240 minutes before dosing)[a]	X		
	00:30 (±5 min)	X		
	01:00 (±5 min)	X		
	02:00 (±15 min)	X		
	04:00 (±30 min)[a]	X		
	06:00 (±30 min)	X		
	08:00 (±30 min)	X		
	12:00 (±30 min)	X		
Day 2	24:00 (±2 hours)	X	X	X
Day 8	168 h		X	X
Day 29 (±7 days)	Predose (within 240 minutes before dosing)[a]	X		
Day 85 (±7 days)	Predose (within 240 minutes before dosing)[a]	X		
Day 197 (±7 days)	Predose (within 240 minutes before dosing)[a]	X		
	04:00 (±30 min)[a]	X		
Day 225 (±7 days)	Predose (within 240 minutes before dosing)[a]	X		

Abbreviations: AT=antithrombin; hh=hours; mm=minutes; PK=pharmacokinetics; TG=thrombin generation
[a] Time point used in population PK analysis.

Table 9 provides a schedule for the collection of pooled urine samples for PK analysis in East Asian patients in the fitusiran arm at East Asian sites. Volume must be recorded.

Table 9: Urine Pharmacokinetic Time Points for East Asian Patients in the Fitusiran Arm at East Asian Sites

Study Day	Protocol Time (hh:mm), Pooled Urine
Day 1	Postdose (0:00) to 06:00 (±30 min)
	06:00 (±30 min) to 12:00 (±30 min)
Day 2	12:00 (±30 min) to 24:00 (±2 hours)

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 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 Operative Procedures

In patients undergoing operative procedures during the treatment period, safety and hemostatic efficacy assessments will be performed according to the Perioperative Schedule of Assessments (described below and outlined in Table 10), 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 10): 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).[12]

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

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

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

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

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

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

[d] Directed physical examination (see Section 7.5.3)

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

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

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

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

[i] Not necessary if captured at preoperative screening.

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

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

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

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

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

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

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

11.4. Bleed Severity Definitions

The definitions of bleed severity are shown in Table 12.

Table 12: Bleed Severity Definitions

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

11.5. Country-Specific Requirements

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

11.6. Protocol Amendment History

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

11.6.1. Amended Protocol 01

Primary changes:

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