SANOFI GENZYME

ALN-AT3SC-002 (SANOFI GENZYME LTE14762)

AN OPEN-LABEL EXTENSION STUDY OF SUBCUTANEOUSLY ADMINISTERED FITUSIRAN IN PATIENTS WITH MODERATE OR SEVERE HEMOPHILIA A OR B WHO HAVE PARTICIPATED IN A PREVIOUS CLINICAL STUDY WITH FITUSIRAN

Final Protocol:	02 June 2015
Amendment 1	30 November 2015
Amendment 2	20 October 2016
Amendment 3	13 June 2017
Amendment 4	09 November 2017
Amendment 5	31 May 2018
Amendment 6	05 March 2019
Amendment 7	25 November 2020
Amendment 8	08 December 2020
Amendment 9	23 June 2021
EUDRACT Number:	2015-001395-21
NCT number:	NCT02554773
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Sponsor:	Genzyme Corporation, 50 Binney Street, Cambridge, MA 02142, USA
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NAMES AND ADRESSES OF:

MONITORING TEAM'S REPRESENTATIVE

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SPONSOR

Name:	Genzyme Corporation
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country-specificity if applicable	Date
Amendment 09	NA	23 June 2021
Amendment 08	NA	08 December 2020
Amendment 07	NA	25 November 2020
Amendment 06	NA	05 March 2019
Amendment 05	NA	31 May 2018
Amendment 04	NA	09 November 2017
Amendment 03	NA	13 June 2017
Amendment 02	NA	20 October 2016
Amendment 01	NA	30 November 2015
Original Protocol	NA	02 June 2015

Amendment 09 (23 June 2021)

This amended protocol 09 (amendment 09) 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

Antithrombin activity level was recently identified as a modifiable target for risk mitigation of vascular thrombosis in patients exposed to fitusiran and the protocol was subsequently amended to introduce a revised fitusiran dose and regimen with the aim of lessening AT reduction.

The overall rationale for the amendment is to extend the study duration for some patients to allow all patients currently in the study to have at least an 18 calendar months period after introduction of the revised dose and regimen (regardless whether the individual patient changed regimen) for purposes of collecting sufficient data for assessment of efficacy and safety of the revised dose and regimen. The study duration will be extended for few patients who would complete the study as per current schedule before having at least 18 calendar months on study after resuming fitusiran under the new dose and regimen.

The whole study duration (till last patient last visit) will not be impacted and the extension will concern only some patients (those who would have completed the study before having this additional follow-up).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Added NCT number and updated amended protocol version to 9.0	Administrative change
Synopsis	Introduced the following text "Some patients will have an extended treatment duration by a maximum of 12 months to ensure all patients will have at least an 18-calendar months treatment period after recent restart with modified SoA and revised fitusiran dose and regimen. This will not affect the whole study duration (last patient last visit is unchanged)."	To extend the study duration for few patients for purposes of collecting sufficient data for assessment of efficacy and safety of the revised dose and regimen.
Table 1 Schedule of assessments (Years 1 to 4), Table 2 Schedule of assessments (Years 5 to 6), Table 3 Modified IMP regimen schedule of assessments (Year 1, 2, 3)	Updated footnoteS of COVID-19 test with the following text:" All study patients that are consenting to this procedure are requested to undergo testing for SARS-CoV-2 (virus responsible for COVID-19), which should include both RT-PCR and antibody testing. Note: Rapid test may be used if RT-PCR is not available. These tests should be performed as early as possible during the study, except for patients who have undergone COVID-19 vaccination, after which antibody testing is no longer required."	To clarify the COVID-19 test requirement in the context of COVID-19 vaccine(s) availability and to allow rapid-test when RT-PCR is not available.
Table 2 Schedule of assessments (Years 5 to 6)	Table title updated to "Schedule of Assessments (Years 5, 6 and 7)"; introduced new columns (M78, M84/EOT) and footnote p for Year 7 assessments.	To accommodate the extension of study duration for few patients following the introduction of revised dose and regimen.
Table 3 Modified IMP regimen schedule of assessments (Year 1, 2, 3)	Added Coagulation assessment in EOS/ET visit.	To correct an omission.
	Footnote "a": updated the study duration in footnote with the following text "The duration that the patient must continue in the study post modified IMP dose/frequency re-start depends on the re-start time-point relative to the overall study start for each individual patient to ensure an overall duration of fitusiran administration of approximately 72 months or 18 calendar months after restarting dosing post dosing pause (whichever is longer). Thus, when the patient reaches the latter of 72 months of study participation or 18 calendar months post dosing restart, the EOT visit should be performed, followed by the EOS and AT follow-up period."	To extend the study duration for few patients for purposes of collecting sufficient data for assessment of efficacy and safety of the revised dose and regimen.

Section # and Name	Description of Change	Brief Rationale
Table 4 Perioperative schedule of assessments in patients undergoing major operative procedures	Introduced a new row for "Hemostatic/Thromboprophylaxis Treatment Plan."	To align with eCRF.
	Updated row of "Perioperative Questionnaire" to "Hemostatic efficacy (Perioperative Questionnaire)" and updated "Perioperative questionnaire" to "Hemostatic efficacy (by using perioperative questionnaire" in footnotes where applicable.	For clarity.
	Added "up to 28 days" following "SDay 28" in the column for postoperative Visit 3.	For clarity.
	Updated footnote "k" with the following text "The date/time of when perioperative hemostatic treatment and thromboprophylaxis (if applicable) coverage was completed will be captured. If hemostatic treatment and thromboprophylaxis are completed at Postoperative Visit 2, the date/time of completion should be recorded, and the SDay 28 visit is not required."	For clarity and facilitate trial operational practice.
Section 1.3.1 Summary of efficacy	Added the following text "Consistent with its intended pharmacologic effects, fitusiran treatment is associated with reductions in AT, increases in thrombin generation, and reductions in number of bleeding episodes."	To update fitusiran efficacy data.
Section 1.3.2 Summary of safety; Section 1.6 benefit-risk assessment	[redacted]	To align with the fitusiran safety updates.
Section 1.3.2 Summary of safety	Removed the text "One death has been reported in a participant with cerebral venous sinus thrombosis (CVST) in ALN-AT3SC-002. In response to this event, the bleed management guidelines were revised in December 2017."	To align with the fitusiran safety updates.
Section 1.4 Study design rational	Introduced the following text "The duration may be longer (up to 7 years) for some patients so that they continue fitusiran treatment for 18 calendar months after introduction of the new dose and regimen into the study."	To extend the study duration for few patients for purposes of collecting sufficient data for assessment of efficacy and safety of the revised dose and regimen.
Section 1.5 Dose rationale	Specified in "Protocol Amendment 07" that introduced the fitusiran revised dose and regimen.	For clarity.
	Revised the language of patients on fitusiran dose "on that dose" to "on either dose, respectively."	To reflect the fitusiran revised dose and regimen.

Section # and Name	Description of Change	Brief Rationale
	Updated "pharmacokinetic/pharmacodynamic (PK/PD) model" with "population pharmacokinetic/pharmacodynamic (popPK/PD) model."	For clarity.
Section 1.6 Benefit-risk assessment	Updated the text on LFT monitoring by including "and provides instruction for the potential discontinuation of fitusiran."	To consider the context of fitusiran on pause.
Section 5.2 Concomitant medications	Included the following text "Use of emicizumab (Hemlibra®) during the study is not permitted."	To clarify that the use of emicizumab (Hemlibra®) during the study is prohibited.
Section 5.3 Management of bleeding episodes with factor or bypassing agents while on fitusiran	Updated the subtitle with the following text: "Bleed management guidelines for patients with AT recovery of ≥60% prior to re-initiation of fitusiran or during a potential fitusiran dose pause."	To consider the context of fitusiran on pause.
	Introduced the following text "During the study period, in case fitusiran is on pause for any reasons and AT activity levels return to approximately 60% (per the central laboratory), patients can initiate regular factor concentrates or BPAs for prophylaxis therapy to prevent spontaneous bleeding episodes, per Investigator discretion in consultation with the study Medical Monitor."	For clarity regarding the use of factor concentrates or BPAs.
Section 5.11 Alcohol restrictions	Introduced a new section on alcohol restrictions as Section 5.11.	To provide definition and criteria for alcohol restriction advise to patients during the study to add clarity on already existing criteria for alcohol use at study entry.
Section 6.1 Study drug	Defined antithrombin (AT) utilized for AT reversal as NIMPs and clarified IMP/NIMP accountability.	To classify AT utilized for AT reversal as NIMP.
Section 6.5 Dose and administration	Removal of fitusiran dosing frequency of "once every month".	To adapt to fitusiran new dose and regimen.
Section 6.5.1.1 LFT criteria for withholding, monitoring and stopping fitusiran dosing	Reworded the language of LFT results by central laboratory and listed prior to other items: "It is preferable that LFT results are to be obtained by Central laboratory. If not available, local laboratory results may be used; however, if a local assessment is drawn, a biochemistry sample must also be drawn for analysis at the central laboratory."	For readability and clarity.
	Modified the text on criteria for reduced predose LFT monitoring considering the patients on monthly dosing schedule following the SoAs or modified IMP regimen SoA.	For clarity.

Section # and Name	Description of Change	Brief Rationale
	Modified “2 months” to “2 consecutive months”, where applicable.	For clarity.
	Introduced the criteria for reduced predose LFT monitoring for patients on a every other month dosing schedule.	For clarity and to accommodate every other month (Q2M) dosing regimen.
Section 6.5.1.3 Antithrombin level criteria for a dose adjustment	Section been updated.	To clarify the requirements for restarting dosing after the dosing pause. And re-organized the text for readability.
Section 6.5.1.3 Fig 1	Added a footnote for Fig 1 “Note: Restart following dosing pause to occur only once centrally measured AT activity levels ≥22%.”	To clarify the rule of dosing restart.
Section 6.5.1.3 Fig 2	Added a footnote: “See rules and exceptions as described above in Section 6.5.1.3. “.	For clarity.
Section 9.1.7.2 Additional Laboratory Assessments	Newly included additional evaluations to be performed for participants undergoing cholecystectomy.	To allow for source data collection to support a better interpretation of biliary-related events.
Section 9.2.7 Adverse Events of Special Interest	Added cross reference to Section 9.1.7.2 regarding the instructions of additional evaluations if participants undergoing cholecystectomy.	For better interpretation/narrative if participant undergo cholecystectomy.
Section 10.2.1 Populations to be Analyzed	Included the following text “All the analysis sets before and after the 2020 dose pause will be populated separately. Accordingly, the statistical analysis will be performed based on each analysis set respectively.”	For clarity and consider the context of fitusiran on pause in the year 2020.
Section 10.2.3 Efficacy analysis	Update the efficacy analysis with the following text “Bleed free duration will be defined as the maximum time intervals between 2 bleeding events and will be analyzed descriptively.”	For clarity.
Section10.2.8 Interim analysis	Specified that the interim analysis will be describe in the SAP.	For clarity.
Section 18.1 Pharmacokinetic assessments time points	In Table 15 and 16, added a footnote regarding the ADA sampling timepoint on PR Months 24 and 36.	For clarity.
Section 18.2.1 Definitions of minor and major surgery	Updated the definition of major dental surgery by including “or any tooth implantation”.	For clarity.
Section 18.5 Contingency measures for a regional or national emergency that is declared by a government agency	Upgraded the appendix for contingency measures for a regional or national emergency as Appendix 18.5, which was originally listed as Appendix 18.6. Subsequent sections have been re-numbered.	Cosmetic, to follow the updated protocol template.

Section # and Name	Description of Change	Brief Rationale
Section 18.6.8 Amended protocol 08	Amendment history of previous version (ie, Amended protocol 08) was newly inserted in the current document Section 18.6 Protocol amendment history.	Administrative change.
Throughout	Added “approximately“ prior to “monthly intervals” of safety FU visits where applicable.	To improve flexibility of patients and facilitate trial operation practice.
Throughout	Added “major” prior to “operative procedure” in perioperative assessment or management where applicable.	For clarity.
Throughout	Used “EQ-5D-5L” instead of “EQ-5D”, “QoL” instead of “QOL”. Abbreviations been updated accordingly.	To correct the typo.
Throughout	Minor editorial, typo error corrections and document formatting revisions.	Minor, therefore, have not been summarized.

PROTOCOL SYNOPSIS

Name of Sponsor: Genzyme Corporation

Name of Investigational Product: Fitusiran (formerly Alnylam ALN-AT3SC henceforth referred to as fitusiran)

Name of Active Ingredient: SAR439774 (formerly ALN-57213)

Title of Study: An Open-label Extension Study of Subcutaneously Administered Fitusiran in Patients with Moderate or Severe Hemophilia A or B who have Participated in a Previous Clinical Study with Fitusiran

Study center(s): This study will be conducted at up to 30 clinical study centers worldwide that have enrolled patients in a previous clinical study with fitusiran.

Phase of development: 1/2

Objectives:

Primary:

- To evaluate the long-term safety and tolerability of fitusiran in male patients with moderate or severe hemophilia A or B

Secondary:

- To investigate the long-term efficacy of fitusiran
- To characterize the safety and efficacy of concomitantly administered Factor VIII (FVIII), Factor IX (FIX) or bypassing agents (BPA) and fitusiran for treatment of bleeding episodes
- To assess changes in health-related quality of life (QoL) over time
- To characterize antithrombin (AT) reduction and thrombin generation (TG) increase
- To characterize the pharmacokinetics (PK) of fitusiran

Exploratory:

- To assess the safety and hemostatic efficacy rating for major operative procedures conducted in patients while on study

Methodology: This is a 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, who previously tolerated dosing in the parent study, ALN-AT3SC-001. ALN-AT3SC-001 is an ongoing Phase 1 study evaluating the safety, tolerability, and PK of fitusiran in healthy subjects and male patients with hemophilia A or B. ALN-AT3SC-001 is being conducted in 4 parts: Part A, a single-ascending dose phase in healthy subjects; Part B, a multiple-ascending dose phase in patients with moderate or severe hemophilia A or B; Part C, an exploratory multiple-dose phase in male patients with moderate or severe hemophilia A or B; and Part D, a multiple-dose phase in patients with moderate or severe hemophilia A or B with inhibitors.

Patients from Part B may roll over into this study after completing Day 70 in the parent study. Patients from Parts C and D are expected to roll over into this study approximately 1 month after completing the 3 monthly doses of study drug in the parent study, thereby maintaining their monthly dosing schedule.

Screening will occur between Day -60 and Day -1. Eligibility for this study will be confirmed before administration of the first dose of study drug. Administration of fitusiran will occur at the clinical study center. Patients will be monitored for 6 hours postdose for the first dose only. At the discretion of the Investigator, contingent upon adequate training after the Month 3 visit, where applicable country and local regulations and infrastructure allow, and if the patient has not previously experienced any severe AEs or SAEs considered related to the study drug that the Investigator and study Medical Monitor believe should preclude the patient from self-administration, patients/caregivers may be trained by the Investigator or a healthcare professional in self-administration. Patients who experience a severe AE or SAE considered related to the study drug that occurs at any time during the study should not self-administer study drug for a 12-week period, unless prior approval is obtained from the study Medical Monitor.

Study assessments will be performed as specified in the Schedule of Assessments (Table 1, Table 2, and Table 3). Fitusiran dosing may occur at home in patients who are trained on self-administration.

For up to 2 years, all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and meet the following criteria for reduced predose LFT monitoring:

a) Did not have any ALT elevation >3× ULN persisting for ≥2 months at any time during the previous 12 months.
b) Did not have any fitusiran doses held due to LFT elevations during the study.

After any modification to the dosing regimen:

a) Did not have any ALT elevation >3× ULN persisting for ≥2 months at any time during the first 12 months under this regimen
b) Must not have had any fitusiran doses held during the first 12 months under this regimen

Safety and efficacy assessments will be performed at the clinical study center at each clinic visit and during an End of Treatment visit. Patients will return to the clinical study center for an End of Study visit 30 days after the last dose of study drug. Separately, follow-up visits to assess AT activity levels should occur at approximately monthly intervals until AT activity level returns to approximately 60% (per the central laboratory), or per Investigator discretion in consultation with the study Medical Monitor (Note: for patients who opt for the commercially available fitusiran, these follow-up visits to assess AT activity level are not required).

Pharmacokinetic assessments will be performed on Day 1, at the Month 12 visit, and at the Month 24 visit (in a subset of patients). Patients will also return to the clinical study center on Day 2 and the day after the Month 12 and Month 24 (in a subset of patients) visits for further PK sampling. Pooled urine collection will also occur at the Month 24 visit in a subset of patients.

In addition, where possible, in patients undergoing major operative procedures while on study, exploratory safety and hemostatic assessments will be performed preoperatively (SDay -3 to SDay -1), intraoperatively (SDay 0), 24 hours postoperatively (SDay 1), and at a postoperative visit occurring 2 to 14 days after the procedure (SDay 2 to SDay 14, per type of procedure). A final postoperative visit will occur on SDay 28 (up to + 28 days) to document the date/time when perioperative hemostatic treatment and thromboprophylaxis (if applicable) coverage was completed.

Bleed events and doses of factor or BPAs administered during the conduct of the study will be recorded in a conventional or patient diary. Safety, quality of life, pharmacodynamic, and pharmacokinetic data will also be collected.

A Safety Review Committee (SRC) will review safety, tolerability, and available PD data, collected during the study with the primary purpose of protecting the safety of patients participating in the study.

Number of patients (planned): Up to 48 patients will be enrolled in this study.

Diagnosis and eligibility criteria: To be enrolled in this study, patients must have moderate or severe hemophilia A or B, previously participated in study ALN-AT3SC-001, and meet the eligibility criteria for this study.

Inclusion criteria:

1. Completed and tolerated study drug dosing in study ALN-AT3SC-001
2. Male aged ≥18 years
3. Moderate or severe, clinically stable hemophilia A or B as evidenced by a laboratory FVIII or FIX level ≤5% at screening. Patients with a FVIII or FIX level >5% at screening will be eligible on provision of a historic laboratory report indicating a trough level ≤5%
4. <deleted per Amendment 1>
5. Willing and able to comply with the study requirements and provide written informed consent

Exclusion criteria:

1. Liver disease defined as any of the following:
   - Clinically significant cirrhosis as determined by the Investigator
   - INR >1.5 at Screening
   - ALT or AST >3× upper limit of the normal (ULN) of the reference range at Screening
   - Platelet count ≤120,000/μL and/or other complete blood count test results that are considered clinically significant and unacceptable by the Investigator
   - Known hepatitis C virus (HCV) infection currently requiring treatment with ribavirin or interferon
2. Known to be human immunodeficiency virus seropositive and have a CD4 count <200 cells/μL at screening (a CD4 result from the previous 6 months may be used to confirm eligibility)
3. History of venous thromboembolism, except for those patients who have a medical history of previous thrombotic event related to permanent indwelling venous access
4. Current serious mental illness that, in the judgment of the Investigator, may compromise patient safety, ability to participate in all study assessments, or study integrity
5. Uncontrolled hypertension (defined as systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥100 mmHg)
6. Corrected QT(QTc) interval ≥450 msec and/or concomitant use of drugs known to prolong the QT/QTc interval at screening
7. Estimated glomerular filtration rate ≤45 mL/min (using the Modification of Diet in Renal Disease formula)

8. Clinically relevant history or presence of cardiovascular, respiratory, gastrointestinal, renal, neurological, inflammatory, or other diseases that, in the judgment of the Investigator, precludes study participation
9. If using nonsteroidal anti-inflammatory drugs intermittently or chronically, must tolerate them with no previous side effects (eg, gastric distress or bleeding)
10. Clinically significant alcohol consumption, as assessed by the Investigator
11. Any condition(s) that, in the opinion of the Investigator, would make the patient unsuitable for enrollment or could interfere with patient participation in or completion of the study

Investigational product, dose and mode of administration: Fitusiran Solution for Injection (subcutaneous [SC] use) is comprised of a synthetic, small interfering ribonucleic acid (siRNA) targeting AT and bearing a triantennary N-acetylgalactosamine (GalNAc) ligand conjugated to the sense strand, formulated in phosphate buffer.

Fitusiran will be administered as a 50 or 80 mg SC injection once monthly or every 2 months according to the dose selection rules in Section 6.5.1 and the SoAs (Table 1, Table 2 and Table 3).

Duration of treatment: It is anticipated that patients in this study will receive treatment with open-label fitusiran for approximately 6 years or until fitusiran becomes commercially available, whichever occurs first. Some patients will have an extended treatment duration by a maximum of 12 months to ensure all patients will have at least an 18-calendar months treatment period after recent restart with modified SoA and revised fitusiran dose and regimen. This will not affect the whole study duration (last patient last visit is unchanged).

Reference therapy, dosage and mode of administration: Not applicable.

Criteria for evaluation:

Safety: Safety assessments will include monitoring for AEs (including serious AEs [SAEs]), clinical laboratory evaluations (including hematology, biochemistry, urinalysis, and coagulation), vital signs, 12-lead electrocardiogram (ECG), antidrug antibodies, and physical examinations.

Efficacy: The efficacy of fitusiran will be evaluated by the following assessments:

- Annualized bleed rate
- Time intervals between bleeding episodes
- Weight-adjusted consumption of FVIII, FIX, or BPA
- QoL assessed by an EQ-5D-5L questionnaire and Haem-A-QoL
- AT levels
- TG levels

Pharmacokinetic Assessments: Blood and urine samples will be collected to assess levels of fitusiran.

Exploratory: Exploratory assessments will include perioperative assessments of safety and hemostatic efficacy rating for major operative procedures conducted while on study.

Statistical methods: The size of this study is not determined via power analysis of particular hypotheses tests. Statistical analyses will be primarily descriptive. Results will be presented in summary tables by starting dose regimen and then by final dose regimen of fitusiran separately for patients with and without inhibitors.

AE summaries will include tabulations of all treatment-emergent AEs (TEAEs), TEAEs by maximum severity, TEAEs by relationship to study medication or underlying hemophilia, SAEs, and AEs

leading to discontinuation of treatment. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment. Laboratory parameter shifts from baseline to worst post-baseline values will be presented. Descriptive statistics will be provided for clinical laboratory data and vital signs. Abnormal physical examination findings, 12-lead ECG data, and antidrug antibody results will be listed by patient (antidrug antibody results will also be tabulated).

Descriptive statistics will be provided for clinical efficacy data. Annualized bleed rate, bleed rate reduction, and percentage reduction compared with pretreatment will be calculated. Descriptive statistics will be presented for the EQ-5D-5L questionnaire, Haem-A-QoL, plasma AT activity, and TG. The total number of patients in each rating category of hemostatic response in patients undergoing operative procedures will be summarized.

Table 1: Schedule of Assessments (Years 1 to 4)

		Treatment Period																																				
		Year 1												Year 2									Year 3								Year 4							
Study Month (Visit)	**Screening**			**M1**	**M2**	**M3**	**M4, M5**[b]	**M6**	**M7, M8**[b]	**M 9**	**M10, M11**[b]	**M12**		**M13, M14**	**M15**	**M16, M17**[b]	**M18**	**M19, M20**[b]	**M21**	**M22, M23**[b]	**M24**		**M25, M26**	**M27**	**M28, M29**[b]	**M30**	**M31, M32**[b]	**M33**	**M34, M35**[b]	**M36**	**M37, M38**	**M39**	**M40, M41**[b]	**M42**	**M43, M44**[b]	**M45**	**M46, M47**[b]	**M48**
Study Day (±Visit Window)	**-60 to -1**	**1**	**2**	**31 ±7**	**61 ±7**	**91 ±7**	**121, 151 ±7**	**181 ±7**	**211, 241 ±7**	**271 ±7**	**301, 331 ±7**	**361 ±7**	**362 ±7**	**391, 421 ±7**	**451 ±7**	**481, 511 ±7**	**541 ±7**	**571, 601 ±7**	**631 ±7**	**661, 691 ±7**	**721 ±7**	**722 ±7**	**751, 781 ±7**	**811 ±7**	**841, 871 ±7**	**901 ±7**	**931, 961 ±7**	**991 ±7**	**1021, 1051 ±7**	**1081 ±7**	**1111, 1141 ±7**	**1171 ±7**	**1201, 1231 ±7**	**1261 ±7**	**1291, 1321 ±7**	**1351 ±7**	**1381, 1411 ±7**	**1441 ±7**
Informed Consent	X																																					
Medical History[a]	X																																					
Demographics	X																																					
Inclusion/ Exclusion Criteria	X																																					
FVIII or FIX Levels	X																																					
Study Drug Administration[b]		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Directed Physical Exam[c]	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X					X				X				X				X
Body Weight	X	X		X	X	X		X		X		X			X		X		X		X									X								X
Vital Signs[d]	X	X		X	X	X		X		X		X			X		X		X		X					X				X				X				X
12-Lead ECG[e]	X	X	X									X	X								X	X								X								X
Liver Status Studies[f]	X, must be performed once at any clinic visit[f]																																					
Inhibitor Status[g]		X										X									X									X								X
Clinical Laboratory Assessment[h, k]	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X					X				X				X				X
Urinalysis[i]	X	X		X	X	X		X		X		X			X		X		X		X					X				X				X				X

Table 1: Schedule of Assessments (Years 1 to 4)

		Treatment Period																																				
		Year 1											Year 2										Year 3								Year 4							
Study Month (Visit)	**Screening**			**M1**	**M2**	**M3**	**M4, M5**[b]	**M6**	**M7, M8**[b]	**M 9**	**M10, M11**[b]	**M12**		**M13, M14**	**M15**	**M16, M17**[b]	**M18**	**M19, M20**[b]	**M21**	**M22, M23**[b]	**M24**		**M25, M26**	**M27**	**M28, M29**[b]	**M30**	**M31, M32**[b]	**M33**	**M34, M35**[b]	**M36**	**M37, M38**	**M39**	**M40, M41**[b]	**M42**	**M43, M44**[b]	**M45**	**M46, M47**[b]	**M48**
Study Day (±Visit Window)	**-60 to -1**	**1**	**2**	**31 ±7**	**61 ±7**	**91 ±7**	**121, 151 ±7**	**181 ±7**	**211, 241 ±7**	**271 ±7**	**301, 331 ±7**	**361 ±7**	**362 ±7**	**391, 421 ±7**	**451 ±7**	**481, 511 ±7**	**541 ±7**	**571, 601 ±7**	**631 ±7**	**661, 691 ±7**	**721 ±7**	**722 ±7**	**751, 781 ±7**	**811 ±7**	**841, 871 ±7**	**901 ±7**	**931, 961 ±7**	**991 ±7**	**1021, 1051 ±7**	**1081 ±7**	**1111, 1141 ±7**	**1171 ±7**	**1201, 1231 ±7**	**1261 ±7**	**1291, 1321 ±7**	**1351 ±7**	**1381, 1411 ±7**	**1441 ±7**
Antidrug Antibodies[j]		X		X	X	X		X		X		X			X		X		X		X									X								X
Plasma PK[l]		X	X									X	X								X	X																
Urine PK[m]																					X	X																
Plasma AT Activity[j, k]		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X					X				X				X				X
Plasma TG[j, k]		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X					X				X				X				X
EQ-5D-5L Questionnaire and Haem-A-QoL[n]		X				X		X		X		X			X		X		X		X									X								X
Patient Education Module Training		To be completed once[o]																																				
Patient Diary		Review with patient at each dosing, and contact every 2 weeks (±4 days) in between fitusiran dosing																																				
Bleed Management Review[p]		Review with patient at each dosing, and contact every 2 weeks (±4 days) in between fitusiran dosing																																				
Perioperative Assessment[q]		Continuous																																				
Adverse Events[r]		Continuous																																				
Concomitant Medications[s]	Continuous																																					

Table 1: Schedule of Assessments (Years 1 to 4)

		Treatment Period																																				
		Year 1												Year 2									Year 3								Year 4							
Study Month (Visit)	**Screening**			M1	M2	M3	M4, M5[b]	M6	M7, M8[b]	M 9	M10, M11[b]	M12		M13, M14	M15	M16, M17[b]	M18	M19, M20[b]	M21	M22, M23[b]	M24		M25, M26	M27	M28, M29[b]	M30	M31, M32[b]	M33	M34, M35[b]	M36	M37, M38	M39	M40, M41[b]	M42	M43, M44[b]	M45	M46, M47[b]	M48
Study Day (±Visit Window)	-60 to -1	1	2	31 ±7	61 ±7	91 ±7	121, 151 ±7	181 ±7	211, 241 ±7	271 ±7	301, 331 ±7	361 ±7	362 ±7	391, 421 ±7	451 ±7	481, 511 ±7	541 ±7	571, 601 ±7	631 ±7	661, 691 ±7	721 ±7	722 ±7	751, 781 ±7	811 ±7	841, 871 ±7	901 ±7	931, 961 ±7	991 ±7	1021, 1051 ±7	1081 ±7	1111, 1141 ±7	1171 ±7	1201, 1231 ±7	1261 ±7	1291, 1321 ±7	1351 ±7	1381, 1411 ±7	1441 ±7
COVID-19 Testing	Anytime during the study[t]																																					

Abbreviations: AE=adverse event; APRI=Aspartate aminotransferase to Platelet Ratio Index; AT=antithrombin; BPA=bypassing agent; CD4=cluster of differentiation 4; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment; EQ-5D-5L=EuroQoL 5-Dimensions, 5-Levels Questionnaire.; ET=Early Termination; exam=examination; FVIII=factor VIII; FIX=factor IX; Haem-A-QoL=Haemophilia Quality of Life Questionnaire; HIV=human immunodeficiency virus; LFT=Liver function test; INR=international normalized ratio; M=Month; PK=pharmacokinetics; PT=prothrombin time; SC=subcutaneous; TG=thrombin generation; treat=treatment.

Notes:

- When scheduled at the same time points, assessments of vital signs and 12-lead ECGs should be performed first, before the physical examinations and blood/urine sample collections.
- Where study assessments overlap with the parent study, the assessments only need to be performed once.
- This schedule applies for patients who continue to receive fitusiran under the 50 or 80 mg monthly dose without meeting criteria for adjusted dosing.

a Any ongoing AEs from the parent study will be captured as medical history. See Section 9.1.1 for details on the medical history/hemophilia history to be recorded at screening.

b SC administration of study drug as per Pharmacy Manual. For up to 2 years, all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1.

c On Day 1, a directed physical examination will be performed at predose and 6 hours postdose. On all other dosing days checked in the table, the directed physical examination will be performed predose. See Section 9.1.5 for assessments to be performed during a directed physical examination.

d Vital signs include blood pressure, heart rate, body temperature (oral, tympanic, or axillary), and respiratory rate. Vital signs will be measured in the seated or supine position after the patient has rested comfortably for 10 minutes. On Day 1, vital signs will be collected predose and at 6 hours (±30 minutes) postdose. On all other dosing days checked in the table, vital signs will be collected predose.

e 12-lead ECGs will be performed in the supine position after the patient has rested comfortably for 10 minutes. 12-lead ECGs will be performed at predose; 30 minutes (±10 minutes) postdose; and 2, 4, and 24 hours (±30 minutes) postdose in relation to the Day 1 and Month 12 fitusiran doses. 12-lead ECGs will be performed at predose; 30 minutes (±10 minutes) postdose; and 2, 4, and 24 hours (±30 minutes) postdose in relation to the Month 24 fitusiran doses. At remaining visits checked in the table, the predose ECG will be performed before blood sample collection.

f Full Hepatic Tests (Table 10) Sample must be performed in all patients once, at Screening (if newly enrolled) or at next scheduled clinic visit (if patient has already completed a clinic visit) and annually thereafter. FibroScan (or FibroTest with APRI) testing must be performed in all patients found to have positive hepatitis C antibody titers

g As determined by Nijmegen modified Bethesda assay.

h Blood samples will be collected predose at visits checked in the table. Biochemistry, hematology, and coagulation are described in Section 9.1.7.1. At Screening, only a complete blood count, platelet count, INR, and CD4 count in HIV seropositive patients is required; however, a CD4 count from the previous 6 months may be used to confirm eligibility.

i Sample for urinalysis will be collected predose at visits checked in the table. Urinalysis parameters are described in Section 9.1.7.3.

j Blood samples will be collected predose at visits checked in the table.

k When patients reinitiate the study at their monthly dose (no dose change) they will have their AT, TG, and coagulation measured monthly for 6 months. Upon the first AT level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the results.

l Blood samples for PK analysis will be collected at the time points listed in Table 13 (Appendix 18.1). Samples collected at the Month 24 visit will be in a subset of patients who opt to participate. There will be no blood samples collected for PK after Month 24.

m In a subset of patients who opt to participate, pooled urine collection will occur at the time points listed in Table 14 (Appendix 18.1). Urine samples for PK will not be collected after Month 24.

n Assessments will be performed predose at visits checked in the table, where available.

o To be completed once, following initiation of the amendment to this protocol (Amendment 4), prior to dosing with fitusiran.

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

q Perioperative assessment of safety and hemostatic efficacy only in patients undergoing major operative procedures while on study (see Table 4).

r AEs including signs and symptoms of thrombosis will be evaluated continuously (see Section 5.5).

s Medication(s) will be recorded as concomitant if any of the following apply: 1) medication is ongoing from a previous fitusiran clinical trial; 2) medication started between a previous fitusiran clinical trial and the present study; or 3) medication started after signing informed consent for the present clinical trial.

t All study patients that are consenting to this procedure are requested to undergo testing for SARS-CoV-2 (virus responsible for COVID-19), which should include both RT-PCR and antibody testing. Note: Rapid test may be used if RT-PCR is not available. These tests should be performed as early as possible during the study, except for patients who have undergone COVID-19 vaccination, after which antibody testing is no longer required. Alternatively, historical test results may be provided under certain circumstances as defined by Sponsor.

Table 2: Schedule of Assessments (Years 5, 6 and 7)

	Year 5		Year 6		Year 7[p]		EOS/ET	
Study Month (Visit)	**M54**	**M60**	**M66**	**M72/EOT**	**M78**	**M84/EOT**	**M73 or M74-M84[p]**	**AT FU**
Study Day (±Visit Window)	**1621 ±7**	**1801 ±7**	**1981 ±7**	**2161 ±7**	**2341 ±7**	**2521 ±7**	**EOT+30 ±7**	**EOT+ 60 ±7**
Study Drug Administration[a, b]	X, monthly							
Directed Physical Exam[c]	X	X	X	X	X	X	X	
Body Weight	X	X	X	X	X	X	X	
Vital Signs[d]	X	X	X	X	X	X	X	
12-Lead ECG[e]		X		X		X	X	
Liver Function Tests[b]	X, monthly[b]							
Liver Status Studies[f]	X, annually at any clinic visit[g]							

Clinical Laboratory Assessment[g, k]	X	X	X	X	X	X	X	
Urinalysis[h]	X	X	X	X	X	X	X	
Antidrug Antibodies[i]		X		X		X		
Inhibitor Status[j]		X		X		X		
Plasma AT Activity[k]	X	X	X	X	X	X	X	X
Plasma TG[k]	X	X	X	X	X	X	X	
EQ-5D-5L Questionnaire and Haem-A-QoL		X		X		X		
Patient Diary	Review with patient at each dosing, and contact every 2 weeks (±4 days) in between fitusiran dosing							
Bleed Management Review[l]	Review with patient at each dosing, and contact every 2 weeks (±4 days) in between fitusiran dosing							
Perioperative Assessment[m]	Continuous							
Adverse Events[n]	Continuous							
Concomitant Medications	Continuous							
COVID-19 Testing	Anytime during the study[o]							

Abbreviations: AE=adverse event; APRI= Aspartate aminotransferase to Platelet Ratio Index; AT=antithrombin; BPA=bypassing agent; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment; EQ-5D-5L=EuroQoL 5-Dimensions, 5-Levels Questionnaire; ET=Early Termination; exam=examination; FU=Follow-up; Haem-A-QoL=Haemophilia Quality of Life Questionnaire for Adults; HIV=human immunodeficiency virus; FVIII=factor VIII; FIX=factor IX; INR=international normalized ratio; LFT=Liver function test; M=Month; PK=pharmacokinetics; PT=prothrombin time; SC=subcutaneous; TG=thrombin generation; treat=treatment.

Notes:

- When scheduled at the same time points, assessments of vital signs and 12-lead ECGs should be performed first, before the physical examinations and blood/urine sample collections.
- This schedule applies for patients who continue to receive fitusiran under the 50 or 80 mg monthly dose without meeting criteria for adjusted dosing.

a SC administration of study drug as per Pharmacy Manual.

b For all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. The frequency of predose LFT monitoring may be decreased to quarterly for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1.

c A directed physical examination will be performed predose on dosing days checked in the table. See Section 9.1.5 for assessments to be performed during a directed physical examination.

d Vital signs include blood pressure, heart rate, body temperature (oral, tympanic, or axillary), and respiratory rate. Vital signs will be measured in the seated or supine position after the patient has rested comfortably for 10 minutes. Vital signs will be collected predose on dosing days checked in the table.

e 12-lead ECGs will be performed in the supine position after the patient has rested comfortably for 10 minutes. ECG will be performed before blood sample collection.

f Full Hepatic Tests (Table 10) must be performed in all patients once annually. FibroScan (or FibroTest with APRI) testing must be performed in all patients found to have positive hepatitis C antibody titers.

g Blood samples will be collected predose on dosing days checked in the table. Biochemistry, hematology, and coagulation are described in Section 9.1.7.1.

h Sample for urinalysis will be collected predose on dosing days checked in the table. Urinalysis parameters are described in Section 9.1.7.3.

i Blood samples will be collected predose on dosing days checked in the table.

j As determined by Nijmegen modified Bethesda assay.

k When patients reinitiate the study at their 80 mg or 50 mg monthly dose (no dose change) they will have their AT, TG, and coagulation measured monthly for 6 months. Upon the first AT activity level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the results.

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

m Perioperative assessment of safety and hemostatic efficacy only in patients undergoing major operative procedures while on study (see Table 4).

n AEs including signs and symptoms of thrombosis will be evaluated continuously (see Section 5.5).

o All study patients that are consenting to this procedure are requested to undergo testing for SARS-CoV-2 (virus responsible for COVID-19), which should include both RT-PCR and antibody testing. Note: Rapid test may be used if RT-PCR is not available. These tests should be performed as early as possible during the study, except for patients who have undergone COVID-19 vaccination, after which antibody testing is no longer required. Alternatively, historical test results may be provided under certain circumstances as defined by Sponsor.

p Only for patients who would complete the study as per current schedule before having at least 18-calendar months treatment under the new dose and regimen. For patients continuing beyond Month 72 for this reason, when 18-calendar months post resuming treatment is reached, the EOT visit should be completed, followed by the EOS and AT follow-up period.

Table 3: Modified IMP Regimen Schedule of Assessments (Year 1, 2, 3)

	Treatment Period																																						
	Year 1													Year 2												Year 3													
Time from modified IMP regimen re-start[a]	**Day of dose re-start**	**PRM1**	**PRM2**	**PRM3**	**PRM4**	**PRM5**	**PRM6**	**PRM7**	**PRM8**	**PRM 9**	**PRM10**	**PRM11**	**PRM12**	**PRM13**	**PRM14**	**PRM15**	**PRM16**	**PRM17**	**PRM18**	**PRM19**	**PRM20**	**PRM21**	**PRM22**	**PRM23**	**PRM24**	**PRM25**	**PRM26**	**PRM27**	**PRM28**	**PRM29**	**PRM30**	**PRM31**	**PRM32**	**PRM33**	**PRM34**	**PRM35**	**PRM36**	**EOS/ET**	**AT FU**
PR Study Day (±Visit Window)	**1**	**29 ±7**	**57 ±7**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**	**365 ±7**	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**	**533 ±7**	**561 ±7**	**589 ±7**	**617 ±7**	**645 ±7**	**673 ±7**	**701 ±7**	**729 ±7**	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**		
Re-sign Informed Consent	X																																						
FVIII or FIX Levels	X																																						
Study Drug Administration Q2M[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		
Study Drug Administration QM[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Directed Physical Exam[c]	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	
Body Weight	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	
Vital Signs[d]	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	
12-Lead ECG[e]	X						X						X												X												X	X	

	Treatment Period																																											
	Year 1														Year 2													Year 3																
Time from modified IMP regimen re-start[a]	**Day of dose re-start**	**PRM1**	**PRM2**	**PRM3**	**PRM4**	**PRM5**	**PRM6**	**PRM7**	**PRM8**	**PRM 9**	**PRM10**	**PRM11**	**PRM12**	**PRM13**	**PRM14**	**PRM15**	**PRM16**	**PRM17**	**PRM18**	**PRM19**	**PRM20**	**PRM21**	**PRM22**	**PRM23**	**PRM24**	**PRM25**	**PRM26**	**PRM27**	**PRM28**	**PRM29**	**PRM30**	**PRM31**	**PRM32**	**PRM33**	**PRM34**	**PRM35**	**PRM36**	**EOS/ET**	**AT FU**
PR Study Day (±Visit Window)	**1**	**29 ±7**	**57 ±7**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**	**365 ±7**	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**	**533 ±7**	**561 ±7**	**589 ±7**	**617 ±7**	**645 ±7**	**673 ±7**	**701 ±7**	**729 ±7**	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**		
Liver Status Studies[f]	X, must be performed once at any clinic visit[f]																																										
Inhibitor Status[g]	X												X											X												X							
Biochemistry and hematology Assessments[h]	X		X		X		X		X		X		X				X				X			X						X						X	X						
Liver function tests[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X						
Urinalysis[j]	X						X						X											X												X	X						
Antidrug Antibodies[k]	X						X						X											X												X							
Coagulation[h]	X	X	X	X	X	X	X	X	X	X	X	X	X				X				X			X				X				X				X	X						
Plasma AT Activity[k]	X	X	X	X	X	X	X	X	X	X	X	X	X				X				X			X				X				X				X	X	X					
Plasma TG[k]	X	X	X	X	X	X	X	X	X	X	X	X	X				X				X			X				X				X				X	X						
EQ-5D-5L Questionnaire and Haem-A-QoL[l]	X						X						X						X					X						X						X							
Patient Education Module Training	To be completed once[m]																																										
Patient Diary	Review with patient at each dosing, and contact every 2 weeks (±4 days) in between fitusiran dosing																																										
Bleed Management Review[n]	Review with patient at each dosing, and contact every 2 weeks (±4 days) in between fitusiran dosing																																										
Perioperative Assessment[o]	Continuous																																										

	Treatment Period																																							
	Year 1													Year 2												Year 3														
Time from modified IMP regimen re-start[a]	Day of dose re-start	PRM1	PRM2	PRM3	PRM4	PRM5	PRM6	PRM7	PRM8	PRM 9	PRM10	PRM11	PRM12	PRM13	PRM14	PRM15	PRM16	PRM17	PRM18	PRM19	PRM20	PRM21	PRM22	PRM23	PRM24	PRM25	PRM26	PRM27	PRM28	PRM29	PRM30	PRM31	PRM32	PRM33	PRM34	PRM35	PRM36	EOS/ET	AT FU
PR Study Day (±Visit Window)	1	29 ±7	57 ±7	85 ±7	113 ±7	141 ±7	169 ±7	197 ±7	225 ±7	253 ±7	281 ±7	309 ±7	337 ±7	365 ±7	393 ±7	421 ±7	449 ±7	477 ±7	505 ±7	533 ±7	561 ±7	589 ±7	617 ±7	645 ±7	673 ±7	701 ±7	729 ±7	757 ±7	785 ±7	813 ±7	841 ±7	869 ±7	897 ±7	925 ±7	953 ±7	981 ±7	1009 ±7		
Adverse Events[p]	Continuous																																						
Concomitant Medications[q]	Continuous																																						
COVID-19 Testing	Anytime during the study[r]																																						

Abbreviations: AE=adverse event; APRI=Aspartate aminotransferase to Platelet Ratio Index; AT=antithrombin; BPA=bypassing agent; CRF=Case Report Form; CD4=cluster of differentiation 4; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment; EQ-5D-5L=EuroQoL 5-Dimensions, 5-Levels Questionnaire.; ET=Early Termination; exam=examination; FVIII=factor VIII; FIX=factor IX; Haem-A-QoL=Haemophilia Quality of Life Questionnaire; HIV=human immunodeficiency virus; LFT=Liver function test; INR=international normalized ratio; M=Month; PK=pharmacokinetics; PR=post-restart; PT=prothrombin time; SC=subcutaneous; TG=thrombin generation; treat=treatment.

Notes:

- When scheduled at the same time points, assessments of vital signs and 12-lead ECGs should be performed first, before the physical examinations and blood/urine sample collections.
- Where study assessments overlap with the parent study, the assessments only need to be performed once.

a This schedule applies for patients meeting criteria for adjusted dosing regimen. Upon each dose adjustment, the patient will restart the schedule (For dose adjustment from 50 mg Q2M to 50 mg QM, the patient will restart at PR M1 as their Month 6 visit under 50 mg will serves as their PR Study Day 1. For dose adjustment from 50 mg QM to 80 mg QM, the patient will restart at PR Study Day 1). The duration that the patient must continue in the study post modified IMP dose/frequency re-start depends on the re-start time-point relative to the overall study start for each individual patient to ensure an overall duration of fitusiran administration of approximately 72 months or 18 calendar months after restarting dosing post dosing pause (whichever is longer). Thus, when the patient reaches the latter of 72 months of study participation or 18 calendar months post dosing restart, the EOT visit should be performed, followed by the EOS and AT follow-up period.

b Patients will follow either the Q2M or QM dosing regimen according to the dose adjustment rules; see Section 6.5.1.3. SC administration of study drug as per Pharmacy Manual. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1.

c On Day 1, a directed physical examination will be performed at predose and 6 hours postdose. On all other dosing days checked in the table, the directed physical examination will be performed predose. See Section 9.1.5 for assessments to be performed during a directed physical examination.

d Vital signs include blood pressure, heart rate, body temperature (oral, tympanic, or axillary), and respiratory rate. Vital signs will be measured in the seated or supine position after the patient has rested comfortably for 10 minutes. On Day 1, vital signs will be collected predose and at 6 hours (±30 minutes) postdose. On all other dosing days checked in the table, vital signs will be collected predose.

e 12-lead ECGs will be performed in the supine position after the patient has rested comfortably for 10 minutes. 12-lead ECGs will be performed before blood sample collection.

f Full Hepatic Tests (Table 9) Sample must be performed in all patients once, at Screening (if newly enrolled) or at next scheduled clinic visit (if patient has already completed a clinic visit) and annually thereafter. FibroScan (or FibroTest with APRI) testing must be performed in all patients found to have positive hepatitis C antibody titers

g As determined by Nijmegen modified Bethesda assay.

h Blood samples will be collected predose at visits checked in the table. Biochemistry, hematology, and coagulation are described in Section 9.1.7.1.

i LFT testing is not required at these visits for patients on the every other month dosing regimen or for patients who meet the criteria for every other month pre-dose LFT monitoring with dosing described in Section 6.5.1.1

j Sample for urinalysis will be collected predose at visits checked in the table. Urinalysis parameters are described in Section 9.1.7.3.

k Blood samples will be collected predose at visits checked in the table. ADA samples will be collected within 240 minutes before dosing according to the schedule in Table 15 and Table 16. At each dose level, upon the first AT activity level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the result.

l Assessments will be performed predose at visits checked in the table, where available.

m To be completed once, prior to dosing with fitusiran.

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

o Perioperative assessment of safety and hemostatic efficacy only in patients undergoing major operative procedures while on study (see Table 4).

p AEs including signs and symptoms of thrombosis will be evaluated continuously (see Section 5.5).

q Medication(s) will be recorded as concomitant if any of the following apply: 1) medication is ongoing from a previous fitusiran clinical trial; 2) medication started between a previous fitusiran clinical trial and the present study; or 3) medication started after signing informed consent for the present clinical trial.

r All study patients that are consenting to this procedure are requested to undergo testing for SARS-CoV-2 (virus responsible for COVID-19), which should include both RT-PCR and antibody testing. Note: Rapid test may be used if RT-PCR is not available. These tests should be performed as early as possible during the study, except for patients who have undergone COVID-19 vaccination, after which antibody testing is no longer required. Alternatively, historical test results may be provided under certain circumstance as defined by Sponsor.

Table 4: Perioperative Schedule of Assessments in Patients Undergoing Major Operative Procedures

	Perioperative Evaluation Period[a]				
	Preoperative Screening	Dental/Surgical Procedure Visit	Postoperative Visit 1	Postoperative Visit 2	Postoperative Visit 3
	SDay -3 to -1	SDay 0	SDay 1[b]	SDay 2 to 14[c]	SDay 28 (up to 28 days)[k]
Hemostatic/ Thromboprophylaxis Treatment Plan	X				
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[g]	X[g]	X[g]
AT Activity Level	X	X[i, h]			
FVIII/IX Levels[g]	X	X[g, h]	X[g]	X[g]	X[g]
Hemostatic efficacy (Perioperative Questionnaire)		X[j, h]	X	X	
Completion of Hemostatic Treatment Coverage				X[k]	X[k]

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; PF=prothrombin fragment; SDay=surgery day; TG=thrombin generation

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

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

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

d Directed physical examination (see Section 9.1.5).

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 10).

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

Table 5: Bleeding Episode Assessments – Unscheduled Visit

	Predose	Postdose 10 min (±5 min)	Postdose 60 min (±5 min)
Directed Physical Examination[a]	X		
Vital Signs	X		
AT	X		
FVIII/IX Levels	X	X	X
TG	X	X	X
Coagulation	X	X	X
Hematology	X	X	X
Optional Imaging[b]	X		

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

a See Section 9.1.5 for assessments to be performed during a directed physical examination.

b 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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPCC	Activated prothrombin complex concentrate
APRI	Aspartate aminotransferase to Platelet Ratio Index
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AT	Antithrombin
AUC	Area under the concentration-time curve
BPA	Bypassing agents
CAT	Calibrated automated thrombogram
CBC	Complete blood count
CD4	cluster of differentiation 4
CFR	Code of Federal Regulation
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus Disease-19
CRO	Contract Research Organization
CVST	Cerebral venous sinus thrombosis
DAA	Direct-acting antiviral
DTP	Direct-to-Patient
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQoL 5-Dimension, 5-Levels Questionnaire
FIX	Factor IX
FVIII	Factor VIII
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
Haem-A-QoL	Haemophilia Quality of Life Questionnaire

Abbreviation	Definition
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IARs	injection associated reactions
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
ISR	Injection site reaction
ISTH	International Society on Thrombosis and Haemostasis
LFTs	Liver function tests
MAD	Multiple-ascending dose
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
NSAID	Nonsteroidal anti-inflammatory drug
NIMP	Non-investigational Medicinal Product
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Prothrombin time
Q2M	every 2 months
QM	every month
QoL	Quality of life
QTc	QT interval corrected for heart rate
rFVIIa	Recombinant factor VIIa
RT-PCR	reverse transcription-polymerase chain reaction
SAD	Single-ascending dose
SAE	Serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviation	Definition
SC	Subcutaneous
SDay	Surgery day
siRNA	Small interfering ribonucleic acid
SRC	Safety Review Committee
SSC	scientific and standardization committee
$t_{½\beta}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TG	Thrombin generation
t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
VTE	Venous thromboembolism

1 INTRODUCTION

1.1 DISEASE OVERVIEW

Hemophilia is an inherited bleeding disorder characterized by a deficiency in blood clotting factors leading to increased risk of bleeding in affected patients (1). People with hemophilia have missing or decreased levels of clotting factors in the intrinsic pathway of coagulation: factor VIII (FVIII) in the case of hemophilia A, and factor IX (FIX) in the case of hemophilia B.

The bleeding severity associated with hemophilia generally correlates with the level of clotting factor, and hemophilia is classified as mild, moderate, or severe based on clotting factor activity relative to normal. Patients with severe hemophilia (factor level <1%) will typically bleed after injury, but also can have frequent spontaneous bleeds, most commonly into muscles and joints (2). Recurrent bleeding into a joint can result in a chronic and disabling arthropathy that is painful and disfiguring, and can markedly impair a patient's mobility and quality of life (QoL) (3).

The coagulation system has evolved to balance the need to maintain hemostasis with the need to prevent thrombosis. This balance is achieved through a well-defined cascade of both procoagulant (eg, FVIII, FIX) and anticoagulant (eg, antithrombin [AT] and protein C) factors. Antithrombin is a liver-expressed natural anticoagulant that is the major endogenous inhibitor of thrombin. Recent studies suggest that the co-inheritance of a deficiency in natural anticoagulants may contribute to a milder phenotype in patients with hemophilia (4, 5). In addition, studies in hemophilic mice demonstrate that the coexistence of AT deficiency resulted in enhanced thrombin generation (TG) as well as a decreased bleeding phenotype in response to injury (6). Therefore, suppression of AT production is being investigated as a potential hemophilia treatment.

Moreover, a proportion of patients treated with replacement factor develop inhibitory antibodies ("inhibitors") to replacement factors that limit effectiveness. Development of inhibitors to infused factor occurs mainly in severe hemophilia, and more frequently in hemophilia A (up to 39% of patients) (7, 8), than in hemophilia B (1% to 3.5% of patients) (9, 10). Once inhibitors are present in high titer (defined as ≥5 Bethesda Units), treatment or prevention of bleeding can become more difficult due to the decreased responsiveness to factor concentrates. In addition, in the case of persons with inhibitors to FIX, anaphylactic reactions and nephrotic syndrome can occur. Treatment of persons with inhibitors consists of both controlling active bleeding by utilizing "bypassing agents" (BPAs; ie, FVIIa or activated prothrombin complex concentrate [aPCC]) as well as attempting to eradicate the inhibitors through immune tolerance induction (ITI) therapy (11). Currently, the treatment of persons with inhibitors with BPA and ITI is both costly and suboptimally effective. The development of inhibitors has been associated with worse musculoskeletal outcomes for persons with hemophilia, diminished quality of life, increased risk of death as well as a markedly increased cost of care (12). Thus, there is a significant unmet need in hemophilia, especially in patients with inhibitors, for novel and improved therapeutic agents that can provide effective prophylactic hemostasis.

1.2 FITUSIRAN (SAR439774)

Fitusiran (SAR439774 [formerly Alnylam ALN-AT3SC]) is an investigational agent comprising a synthetic small interfering ribonucleic acid (siRNA) covalently linked to a triantennary N-acetyl galactosamine (GalNAc) ligand, designed to suppress liver production of AT as a strategy to rebalance the coagulation cascade, thereby improving TG and hemostasis in individuals with hemophilia.

The initial proposed indication for fitusiran is for the treatment of patients with hemophilia A or hemophilia B. Pharmacology data in mouse models of hemophilia support the therapeutic hypothesis for fitusiran. Specifically, administration of fitusiran has been shown to increase TG in both wild type and hemophilia models and to improve hemostasis in models of hemophilia. The nonclinical pharmacology, pharmacokinetics (PK), and toxicology of fitusiran were evaluated in a series of in vitro and in vivo studies that have enabled chronic dosing in clinical studies.

A summary of the nonclinical data is in the fitusiran Investigator's Brochure (IB).

1.3 CLINICAL DEVELOPMENT

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

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

1.3.1 Summary of Efficacy

In Phase 1/2 clinical trials, monthly dosing with fitusiran in patients with hemophilia A and B, with or without inhibitors resulted in sustained antithrombin lowering and improved hemostasis as measured by reductions in patients' annualized bleeding rate (ABR) (13, 14). Consistent with its intended pharmacologic effects, fitusiran treatment is associated with reductions in AT, increases in thrombin generation, and reductions in number of bleeding episodes.

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

1.3.2 Summary of Safety

[redacted].

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

1.3.3 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=11), respectively. AT reduction was maintained in this study (ALN-AT3SC-002), with mean maximal AT reduction of 83.6% for 50 mg (N=13) and 85.9% for 80 mg (N=21) as of 08 August, 2017.

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

1.4 STUDY DESIGN RATIONALE

This is a 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, who have previously tolerated dosing in a clinical study with fitusiran. Both nonclinical and clinical data support the continuation of fitusiran treatment in this long-term extension study.

Safety and efficacy assessments will be performed periodically as outlined in the Schedule of Assessments (Table 1, Table 2 and Table 3) to continue to assess the effect of fitusiran beyond the duration of the ongoing clinical studies, and will enable patients who have completed dosing in a prior study with fitusiran (provided eligibility criteria for this study are met) to continue to receive fitusiran. This study will allow patients to receive treatment with fitusiran for approximately 6 years or until fitusiran becomes commercially available, whichever occurs first. The duration may be longer (up to 7 years) for some patients so that they continue fitusiran treatment for 18 calendar months after introduction of the new dose and regimen into the study.

1.5 DOSE RATIONALE

Patients enrolled in this study were initially administered subcutaneous (SC) fitusiran once every month where 1 month has been defined as 30 days to aid in patient compliance with the long-term dosing regimen. Patients started the study on weight-based doses then transitioned early on to a 50 mg- or 80 mg-fixed monthly dose depending on what they received in the parent study.

A once-monthly dosing regimen is supported by preliminary results from clinical and nonclinical studies. Data from the parent study (ALN-AT3SC-001) suggest that a reduction in AT levels is sustained for up to 60 days following a single dose of fitusiran. Additionally, preliminary data in nonhuman primates suggest that steady-state AT suppression can be achieved and maintained after monthly doses of fitusiran.

A change in the fitusiran dosing regimen has been introduced as a risk mitigation measure for vascular thrombotic events in Protocol Amendment 07. As the risk of vascular thrombotic events is thought to be increased in the setting of low AT activity levels, a reduced dose of 50 mg administered SC once every 2 months has been selected to minimize the occurrence of AT activity levels below 10%. At a reduced dose of 50 mg every 2 months, if a patient has more than 1 AT level <15%, the patient will be required to permanently discontinue fitusiran. Patients previously exposed to fitusiran at a dose of 50 mg monthly or 80 mg monthly with no more than 1 AT activity level <15% at any time during fitusiran treatment (based on at least 3 months of prior AT measurements) may have the option to remain on either dose, respectively.

If a patient receiving fitusiran 50 mg once every 2 months has 2 steady state AT levels above 35%, the patient will be dose escalated to fitusiran 50 mg monthly. In very rare cases, if a patient still has 2 steady state AT levels above 35% at the 50 mg monthly dose, the patient will escalate to the 80 mg monthly dose. Details are described in Section 6.5.1.3.

1.6 BENEFIT-RISK ASSESSMENT

Based on the available clinical data (see Section 1.3), fitusiran may be able to offer potentially reduced bleeding rates for patients receiving factor concentrate or BPA treatment prophylactically or on-demand. Further, the pharmacodynamic profile of fitusiran results in consistent reduction of AT and therefore may provide more consistent increase in thrombin generation and hemostatic protection throughout the dosing interval. The clinical experience to date suggests that in hemophilia A or B patients, with or without inhibitors, fitusiran treatment is associated with reductions in AT, increases in thrombin generation, and reduction of the number of bleeding episodes.

[redacted] The risk of vascular thrombotic events is thought to be elevated in patients receiving fitusiran with AT activity levels <10%. In addition, the concomitant treatment of breakthrough bleeding episodes with factor or BPA, particularly at doses higher than recommended in the protocol may confer an increased risk of thrombotic events. Additional details regarding the benefits and risks of fitusiran are provided in the Investigator's Brochure.

This clinical protocol has exclusion criteria intended to minimize the risk of thrombosis, [redacted]. With respect to the risk of thrombosis, the protocol includes a change in the fitusiran dosing regimen to minimize the occurrence of AT levels <10% (Section 6.5.1.3), detailed guidance and oversight on treatment of breakthrough bleeding episodes with reduced factor and/or BPA dosing (Section 5.3), and monitoring and management of thrombosis while patients are on fitusiran (Section 5.7). The protocol stipulates ongoing monitoring for elevated transaminases (Section 6.5.1.1) and provides instruction for the potential discontinuation of fitusiran. The safety of trial patients will be overseen by a Safety Review Committee (Section 3.4).

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the long-term safety and tolerability of fitusiran in male patients with moderate or severe hemophilia A or B.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To investigate the long-term efficacy of fitusiran
- To characterize the safety and efficacy of concomitantly administered FVIII, FIX, or BPA and fitusiran for treatment of bleeding episodes
- To assess changes in health-related QoL over time
- To characterize AT reduction and TG increase
- To characterize the PK of fitusiran

2.3 EXPLORATORY OBJECTIVES

The exploratory objective of this study is:

- To assess safety and the hemostatic efficacy rating for operative procedures conducted in patients while on study

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN

This is a Phase 1/2 multicenter, multinational, open-label extension study, conducted at up to 30 clinical study centers worldwide, to evaluate the long-term safety and efficacy of fitusiran in male patients with moderate or severe hemophilia A or B, who previously tolerated dosing in Part B, Part C or Part D of the parent study, ALN-AT3SC-001.

Patients from Part B may roll over into this study after completing Day 70 in the parent study. Patients from Parts C and D are expected to roll over into this study approximately 1 month after completing the 3 monthly doses of study drug in the parent study, thereby maintaining their monthly dosing schedule.

Screening will occur between Day -60 and Day -1. Eligibility for this study will be confirmed before administration of the first dose of study drug. Administrations of fitusiran will occur at the clinical study center or may be self-administered at home under the conditions described below. Patients will be monitored for 6 hours postdose for the first dose only.

At the discretion of the Investigator, contingent upon adequate training after the Month 3 visit, where applicable country and local regulations allow, and if the patient has not previously experienced any severe AEs or SAEs considered related to the study drug that the Investigator and study Medical Monitor believe should preclude the patient from self-administration, the patient/caregiver may be trained by the Investigator or healthcare professional in self-administration. For up to 2 years, all fitusiran dosing, liver function test (LFT) results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1. Safety and efficacy assessments will be performed at time points specified in Table 1, Table 2 and Table 3. Unscheduled visits for study assessments may occur if deemed necessary by the study personnel. In addition, patients who complete the study or discontinue treatment will continue to have safety assessments and AT activity levels monitored at time points specified in Table 1, Table 2 and Table 3 following the final fitusiran dose until AT activity levels return to approximately 60% (per the central laboratory), or per Investigator discretion in consultation with the study Medical Monitor (Note: for patients who opt for the commercially available fitusiran, these follow-up visits to assess AT activity level are not required).

Pharmacokinetic and urine assessments will be performed at clinic visits on Day 1 and Month 12, and on Month 24 (in subset of patients). Patients will also return to the clinical study center on Day 2 and the day after Month 12 and Month 24 (in subset of patients) visits for further PK sampling. Also, pooled urine collection will occur on Month 24 in a subset of patients.

Where possible, in patients undergoing major operative procedures while on study, safety and hemostatic efficacy assessments will be performed preoperatively (SDay -3 to SDay -1), intraoperatively (SDay 0), 24 hours postoperatively (SDay 1), and a postoperative visit 2 to 14 days after the procedure (SDay 2 to SDay 14, per type of procedure). A final postoperative

visit will occur on SDay 28 (up to + 28 days) to document the date/time when perioperative hemostatic and thromboprophylaxis (if applicable) treatment coverage was completed.

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

3.2 NUMBER OF PATIENTS

Up to 48 patients with moderate or severe hemophilia A or B who have previously participated in the parent study (ALN-AT3SC-001) may be enrolled if they meet the eligibility criteria for this study.

3.3 TREATMENT ASSIGNMENT

Patients enrolled in this study will receive open-label fitusiran.

After confirming eligibility, patients will be assigned a patient number that corresponds to or can be mapped to their current patient number on the parent study.

3.4 SAFETY REVIEW COMMITTEE

The SRC will review safety, tolerability, and available PD data, collected during the study with the primary purpose of protecting the safety of patients participating in the study. The SRC will be comprised of the PI from each clinical study center with a patient currently in the study (either dosed or about to be dosed) or their designee, an independent hematologist with experience caring for patients with hemophilia, the study Medical Monitor, and the Contract Research Organization (CRO) Medical Monitor. The SRC will meet at approximately every 3 to 6 months, and on an ad hoc basis, as required. Further details will be specified in the SRC Charter.

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.

3.5 DOSE ADJUSTMENT CRITERIA

Following SRC review, the dose may be adjusted (increased or decreased) for the entire study population if emerging safety and tolerability data support a more optimal dose.

Additionally, the SRC, or the treating Principal Investigator (PI), may authorize dose adjustments for individual patients based on safety, tolerability, and available PD response data. Dose adjustment criteria are detailed in Section 6.5.1. Study drug administration for individual patients may be paused if an SAE reported is considered related to study drug, including venous thromboembolism (VTE). The SRC will be consulted before restarting study drug administration in individual patients.

Instructions for AT-driven fitusiran regimen modification are provided in Section 6.5.1.3.

3.6 CRITERIA FOR STUDY TERMINATION

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

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 INCLUSION CRITERIA

To be enrolled in the study, patients must meet the following criteria before administration of the first dose of fitusiran:

1. Completed and tolerated study drug dosing in study ALN-AT3SC-001
2. Male aged ≥18 years
3. Moderate or severe, clinically stable hemophilia A or B as evidenced by a laboratory FVIII or FIX level ≤5% at screening. Patients with a FVIII or FIX level >5% at screening will be eligible on provision of a historic laboratory report indicating a trough level ≤5%
4. <Removed per Amendment 1>
5. Willing and able to comply with the study requirements and provide written informed consent

4.2 EXCLUSION CRITERIA

1. Liver disease defined as any of the following:

- Clinically significant cirrhosis as determined by the Investigator
- International normalized ratio (INR) >1.5 at Screening
- ALT or AST >3× ULN of the reference range at Screening
- Platelet count ≤120,000/µL and/or other complete blood count (CBC) test results that are considered clinically significant and unacceptable by the Investigator
- Known hepatitis C virus (HCV) infection currently requiring treatment with ribavirin or interferon

2. Known to be human immunodeficiency virus (HIV) seropositive and have a CD4 count <200 cells/µL at screening (a CD4 result from the previous 6 months may be used to confirm eligibility)
3. History of VTE, except for those patients using inhibitors who have a medical history of previous thrombotic event related to permanent indwelling venous access.
4. Current serious mental illness that, in the judgment of the Investigator, may compromise patient safety, ability to participate in all study assessments, or study integrity
5. Uncontrolled hypertension (defined as systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥100 mmHg)
6. Corrected QT (QTc) interval ≥450 msec and/or concomitant use of drugs known to prolong the QT/QTc interval at Screening

7. Estimated glomerular filtration rate [eGFR] ≤45 mL/min (using the Modification of Diet in Renal Disease formula [MDRD])
8. Clinically relevant history or presence of cardiovascular, respiratory, gastrointestinal, renal, neurological, inflammatory, or other diseases that, in the judgment of the Investigator, precludes study participation
9. If using nonsteroidal anti-inflammatory drugs (NSAIDs) intermittently or chronically, must tolerate them with no previous side effects (eg, gastric distress or bleeding)
10. Clinically significant alcohol consumption, as assessed by the Investigator
11. Any condition(s) that, in the opinion of the Investigator, would make the patient unsuitable for enrollment or could interfere with patient participation in or completion of the study

4.3 WITHDRAWAL CRITERIA

Patients are free to discontinue from study treatment or withdraw from the study at any time and for any reason, without penalty to their continuing medical care. There will be no replacements of patients who withdraw from this study.

The Investigator may withdraw a patient from the study for any of the following reasons:

- Protocol violation
- AE
- Use of, or need for, a prohibited medication (Note: Before discontinuation, the Investigator should consult with the study Medical Monitor to determine if withdrawal is warranted.)
- Physician decision
- Patient decision (withdrawal of consent)
- Patient is considerably noncompliant with the protocol-required fitusiran dosing visits

The Investigator will also withdraw the patient from the study upon the request of the Sponsor or if the Sponsor terminates the study.

Upon occurrence of a serious or intolerable AE, the Investigator will make every possible attempt to confer with the Sponsor before withdrawing the patient.

Missing an occasional dose of fitusiran will not necessarily result in the patient being withdrawn from the study. However, if a patient misses multiple consecutive doses of fitusiran, the Investigator at the clinical study center and the study Medical Monitor will determine whether the patient should be withdrawn from the study.

When a patient withdraws or is withdrawn from the study, an Early Termination visit should occur 30 days following the patient's last dose. Separately, follow-up visits to assess AT activity levels should occur at approximately monthly intervals until AT activity level returns to

approximately 60% (per the central laboratory) (Note: for patients who opt for the commercially available fitusiran, these follow-up visits to assess AT activity level are not required). For patients who withdraw early, at least 2 attempts will be made to contact the patient to complete an Early Termination visit.

In the event a patient withdraws or is withdrawn from the study, the Investigator will inform the Sponsor immediately.

If the patient withdraws or is withdrawn from the study, the reason will be noted in the patient medical record and on the electronic Case Report Form (eCRF).

4.4 CRITERIA FOR TEMPORARILY DELAYING ADMINISTRATIONS OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Section 18.5 for patient visits and/or administration of study intervention.

5 TREATMENT OF PATIENTS

5.1 DESCRIPTION OF STUDY DRUG

A description of the investigational product is provided in Table 7.

Table 7: Investigational Product

	Investigational Product
Product Name:	Fitusiran
Dosage Form:	Sterile solution packaged in 2-mL Type I glass vials or prefilled syringes[a]
Route of Administration	Subcutaneous
Physical Description	Fitusiran Solution for Injection (SC use) is an siRNA targeting AT and bearing a triantennary GalNAc ligand conjugated to the sense strand, formulated in phosphate buffer.

Abbreviations: AT = antithrombin; GalNAc = N-acetylgalactosamine; SC = subcutaneous; siRNA = small interfering ribonucleic acid.

a Study drug may be provided in prefilled syringes either at the clinic (healthcare setting) or in a nonhealth care setting (home injection) in a subset of patients receiving 80 mg monthly dose of fitusiran. The patient will be trained on prefilled syringe self-administration. Patients who have missed more than 6 consecutive fitusiran doses for any reason should utilize the study drug provided as a vial and syringe for at least 3 injections prior to utilizing prefilled syringe.

5.2 CONCOMITANT MEDICATIONS

Use of concomitant medications will be recorded on the patient's eCRF as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3). 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.

Treatment for hemophilia must be "on demand." Importantly, patients should not use factor concentrates as prophylaxis for bleeding episode prevention, including doses related to anticipated hemostatic challenges such as physical activity, after Day 7 on fitusiran. For prophylaxis of bleeding episodes in patients who require major operative procedures see Section 5.7.

Concomitant use of drugs known to prolong the QT/QTc interval should be avoided.

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. Use of emicizumab (Hemlibra®) during the study is not permitted.

If patients use NSAIDs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

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

For patients with known HCV infection, concurrent treatment with ribavirin or interferon is not permitted during fitusiran treatment. In patients without cirrhosis or HBV-coinfection, concurrent treatment of HCV with direct-acting antiviral (DAA) therapy may be permitted after review and approval of the individual treatment plan by the study Medical Monitor.

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 administered 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.

5.3 MANAGEMENT OF BLEEDING EPISODES WITH FACTOR OR BYPASSING AGENTS WHILE ON FITUSIRAN

Investigators will establish and provide instructions for an individualized bleed management plan based on the guidelines in Table 8 for each patient.

The bleed management plan should be reviewed by the Investigator or designee with the patient at each dosing (and via telephone contact every 2 weeks [±4 days] between fitusiran dosing) and updated as necessary.

Initiation of fitusiran treatment results in a progressive lowering of AT levels over 4 weeks.

Guidelines are provided below for patients newly initiating therapy or re-initiating therapy, and during continuous therapy with fitusiran.

Bleed management guidelines for patients with AT recovery of ≥60% prior to re-initiation of fitusiran or during a potential fitusiran dose pause

AT recovery is defined as AT activity level of approximately 60% or greater (per the central laboratory).

After initiating therapy with fitusiran, it is recommended that patients call the Investigator prior to dosing with factor or BPA, and must call for any repeat doses of FVIII, FIX, aPCC, or for the third or subsequent dose of rFVIIa.

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 participants will have AT activity lowering of >50%, with a median value of 66.8%. Based on these AT kinetics, it is recommended that patients continue with their standard factor/BPA regimens for the first week following re-initiation of fitusiran dosing, with institution of the protocol-specific bleed management guidelines with reduced factor/BPA starting the second week after re-initiation, as described below and in Table 8.

During the study period, in case fitusiran is on pause for any reason and AT activity levels return to approximately 60% (per the central laboratory), patients can initiate regular factor concentrates or BPAs for prophylaxis therapy to prevent spontaneous bleeding episodes, per Investigator discretion in consultation with the study Medical Monitor.

Bleed management guidelines for Week 2 and beyond, and for patients with AT recovery of <60% prior to re-initiation of fitusiran:

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 perform assessments per Section 5.4 and Table 5.
2. If a determination is made that symptoms require treatment, the recommended treatment algorithm for bleeding episodes is described below:
3. A single dose can be administered according to the guidelines in Table 8.
4. 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.
5. 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 contact 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 5.4 and Table 5).
    b) If more than two doses of FVIII, FIX or aPCC or three doses of rFVIIa are needed, the patient to be seen at the study center within 48-72 hours.
6. Doses should not be administered at less than 24-hour intervals (except rFVIIa as indicated in Table 8).
7. Doses should not exceed the protocol maximum recommended dose indicated in Table 8.

8. 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 8
   b) Dosing of factor or BPA at decreased intervals than those recommended in Table 8
   c) Multiple or repeated doses of factor or BPA
9. Antifibrinolytics may not be used in combination with factor or BPA.

Table 8: Bleed Management Dosing Guidelines by Specific Product

	Factor VIII	Factor IX Standard half-life	Factor IX Extended half-life	aPCC	Recombinant Factor VIIa
Recommended <u>single</u> dose of	10 IU/kg	20 IU/kg	20 IU/kg	30 U/kg	≤45 µg/kg
Single dose should not exceed	20 IU/kg	30 IU/kg	30 IU/kg	50 U/kg	45 µg/kg
Repeat dose instructions	Mandatory to call the clinical study center prior to second dose Consider evaluation and treatment at the clinical study center (see Section 5.4)				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 Assessment 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 rFVIIa and aPCC are included for completeness. Adjunctive management of bleeding episodes should be carried out per standard of care. It is expected that these non-inhibitor patients will be routinely managed with FVIII and FIX.

5.4 ASSESSMENT OF COAGULATION PARAMETERS AT THE TIME OF A BLEED

If a patient presents at 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 5.

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 post-dose assessments in Table 5 should be obtained in a single draw at any time during the visit.

5.5 MONITORING AND MANAGEMENT OF THROMBOTIC EVENTS

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

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

If a patient develops 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 9.2.7 for further information regarding Adverse Events of Special Interest).

5.6 USE OF FACTOR OR BPA FOLLOWING DISCONTINUATION OF FITUSIRAN

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

5.7 ELECTIVE AND/OR EMERGENCY SURGERY

If an urgent need for major surgery arises during the study period, the study Medical Monitor will be informed, and 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 18.2 (Section 18.2.1) for definitions of minor and major surgery.

Perioperative Treatment Plan

In all patients undergoing major surgery, a written perioperative treatment plan will be reviewed with the study Medical Monitor before conducting the procedure, unless clinical circumstances do not allow. The perioperative treatment plan should be developed using the same principles as bleed management described in Section 5.3 and the guideline below:

- If the clinical circumstance is such that the recommended factor or BPA doses and/or dose intervals in Table 8 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 18.2 (Section 18.2.1) 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 an 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 major surgery during the study as described in Section 8.4, and as scheduled in Table 4.

5.8 MANAGEMENT OF SEPSIS

Formal clinical guidelines do not currently recommend correction of low AT that is seen in the setting of sepsis, citing a lack of evidence for improved outcomes and an increased risk of bleeding (16, 17). If a clinical determination is made that AT correction is desirable for an fitusiran-treated patient in the setting of sepsis, this may be initiated per Investigator discretion.

5.9 TREATMENT COMPLIANCE

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses multiple consecutive doses, the Investigator, in consultation with the CRO Medical Monitor, will discuss whether the patient will be able to continue on the study.

5.10 RANDOMIZATION AND BLINDING

The study is an open-label, nonrandomized design.

5.11 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.

6 STUDY DRUG MATERIALS AND MANAGEMENT

6.1 STUDY DRUG

Investigational Medicinal Product (IMP):

Fitusiran Solution for Injection (SC use) will be supplied as a sterile solution in vials or prefilled syringes. Detailed information describing the preparation, administration, and storage of fitusiran is provided in the Pharmacy Manual.

Non-investigational Medicinal Product (s) (NIMPs):

For antithrombin reversal refer to Section 5.5.

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

All study drug must be dispensed by the Investigator or designee as defined in the Pharmacy Manual. The IMP/NIMP may be supplied at the site or from the Investigator/site/Sponsor to the patient via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the patient.

In case of a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 18.5.

6.2 STUDY DRUG PACKAGING AND LABELING

All packaging, labeling, and production of IMP will be in compliance with Good Manufacturing Practice specifications, as described in the Manufacture of Investigational Medicinal Products Volume 4 Annex 13, and any other or local applicable regulations.

The IMP labels and external packaging will include all appropriate information as per local labeling requirements. Sample labels will be submitted to health authorities, per local country submission requirements.

6.3 STUDY DRUG STORAGE

Study drug will be stored per the labeled instructions. Any deviation from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee.

No special procedures for the safe handling of fitusiran are required.

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

Study drug supplied for this study may not be administered to any person not enrolled in the study.

Additional storage details are provided in the Pharmacy Manual.

6.4 STUDY DRUG PREPARATION

Qualified staff at each clinical study center or the home healthcare professional (where available) who may dispense study drug to the patient for self-administration will be responsible for preparation of fitusiran doses, according to procedures detailed in the Pharmacy Manual. Patients and/or caregivers may also prepare fitusiran doses after receiving proper instruction.

6.5 DOSE AND ADMINISTRATION

Patients will be administered fitusiran as an SC injection for the duration of the study. Initially, based on the parent study dosing paradigm, it is expected that the starting dose administered in this study will be 0.225 mg/kg. Either fixed or weight-based doses may be given, provided that the dose is no greater on a weight basis than the highest dose determined to be safe and well tolerated in the parent study (ALN-AT3SC-001). Following review of safety and tolerability data, the dose may be modified, for individual patients or for the entire study population, if emerging data support a more optimal dose and dosing regimen.

If the patient has not previously experienced any severe AEs or SAEs considered related to the study drug that the Investigator and study Medical Monitor believe should preclude the patient from self-administration, the patient/caregiver may be trained by the Investigator or healthcare professional in self-administration, permitted to occur from Month 3 forward.

Patients who experience a severe AE or SAE considered related to the study drug that occurs at any time during the study should not self-administer study drug for a 12-week period, unless prior approval is obtained from the study Medical Monitor.

Patients with elevated liver transaminases will be further evaluated at a clinic visit prior to permitting self-administration of study drug. Once considered asymptomatic and if liver transaminases are returning towards normal, patients may be permitted to self-administer study drug at Investigator discretion. For up to 2 years, all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1.

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

Pre-filled Syringe with Safety System:

Study drug may be provided in prefilled syringes either at the clinic (healthcare setting) or in a nonhealth care setting (home injection) in a subset of patients receiving 80 mg SC injection once monthly. The patient will be trained on prefilled syringe self-administration. The Investigator and/or delegated designee will complete a treatment process with the patient and/or patient's caregiver to prepare and administer the injection using the pre-filled syringe with safety system for monthly injections. The first injection is given by the Investigator and/or delegated designee while teaching patient and/or caregiver on how to perform the injection. The second injection is performed by patient or caregiver under the supervision of the Investigator and/or delegated designee. Once patient or caregiver has completed the required training and the Investigator and/or delegated designee approves, patient or caregiver may prepare and self-administer the subsequent injection at home. Patients who have missed more than 6 consecutive fitusiran dose for any reason should utilize the study drug provided as a vial and syringe for at least 3 injections prior to utilizing prefilled syringe.

6.5.1 Dose Modifications

If a study drug-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, at which time the study Medical Monitor should be contacted.

6.5.1.1 LFT Criteria for Withholding, Monitoring and Stopping Fitusiran Dosing

1. It is preferable that LFT results are to be obtained by Central laboratory. If not available, local laboratory results may be used; however, if a local assessment is drawn, a biochemistry sample must also be drawn for analysis at the central laboratory.
2. For patients following the SoAs in Table 1 and Table 2:
   a) For up to 2 years, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose of fitusiran.
   b) From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and who meet following specific criteria:
   - Did not have any ALT elevation >3× ULN persisting for ≥2 consecutive months at any time during the previous 12 months.
   - Did not have any fitusiran doses held due to LFT elevations during the study.

   Note: negative Hep C patients include patients who never met HCV, ie, antibodies are negative, but also those with only positive antibodies without any viral load detected (ie, patient has cleared the infection, but antibodies still detected as positive). To confirm this eligibility, patients who cleared Hep C infection must have documented sustained negative virologic load.
3. For patients on a monthly dosing schedule following the SoA in Table 3 (modified IMP regimen SoA), monthly predose LFT testing is not required if the criteria for reduced predose LFT monitoring is met as described below:

- Did not have any ALT elevation >3× ULN persisting for ≥2 consecutive months at any time during the first 12 months under this regimen.
- Must not have had any fitusiran doses held during the first 12 months under this regimen.

4. For patients on a every other month dosing schedule following the SoA in Table 3 (modified IMP regimen SoA), monthly testing is required for the first 12 months under the dosing regimen. After the first year, predose LFT testing is only required every other month prior to dosing.
5. For any ALT elevation >3× ULN or >3× Baseline (for those with elevated baseline values), central laboratory results should be used to guide subsequent monitoring as detailed in Table 9.
6. For any ALT elevation >3× ULN or >3× Baseline (for those with elevated baseline values) (Table 9):
   a) Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   a) Perform assessments per Table 10 and Table 11.
   b) If an alternative cause is found, provide appropriate care.
7. For any ALT elevation >3× ULN or >3× Baseline without alternative cause see Table 9 below:

Table 9: Monitoring and Dosing Rules for Patients with Confirmed ALT Elevations >3× ULN or >3× Baseline with No Alternative Cause Identified

Transaminase Level	HCV RNA Negative Patients with Normal Baseline ALT	HCV RNA Negative Patients with Elevated Baseline ALT[a]	HCV RNA Positive Patients with Normal Baseline ALT	HCV RNA Positive Patients with Elevated Baseline ALT[a, b]
>3× to 5×ULN or Baseline	Discontinue dosing when ALT>3×ULN if patient is symptomatic[c], TBL ≥2×ULN, or INR >1.5. Otherwise, may continue dosing with biweekly[d] monitoring including hematology, biochemistry, LFT, and coagulation per Table 10. If elevation persists for ≥2 months, must discuss with the study Medical Monitor before continuing dosing.	Discontinue dosing when ALT >3× Baseline or >300 U/L (whichever comes first) if patient is symptomatic[c], TBL >2×ULN, or INR >1.5. Otherwise, may continue dosing with biweekly[d] monitoring including hematology, biochemistry, LFT, and coagulation per Table 10. If elevation persists for ≥2 months, must discuss with the study Medical Monitor before continuing dosing.		Discontinue dosing when ALT >3× Baseline or >300 U/L (whichever comes first) if patient is symptomatic[c], TBL >2× ULN, or INR >1.5. Otherwise, may continue dosing with biweekly[d] monitoring including hematology, biochemistry, LFT, and coagulation per Table 10. If elevation persists for ≥2 months, must discuss with the study Medical Monitor before continuing dosing.
>5× to 8× ULN or Baseline	Hold[e] dose if ALT >5×ULN until ALT ≤1.5×ULN. Monitoring at least weekly until ALT declining on two consecutive draws, then monitoring biweekly[d], including hematology, biochemistry, and coagulation per Table 10.		Discontinue dosing when ALT >5×ULN if patient is symptomatic[c], TBL >2×ULN or INR >1.5. Otherwise, biweekly[d] monitoring including hematology, biochemistry, LFT, and coagulation per Table 10. If elevation persists for ≥2 months, must discuss with the study Medical Monitor before continuing dosing.	
>8× ULN or Baseline	Discontinue dosing after confirmation if ALT >8×ULN	Discontinue dosing after confirmation if ALT >8×Baseline or >500 U/L (whichever comes first).	Discontinue dosing after confirmation if ALT >8×ULN.	Discontinue dosing after confirmation if ALT >8×Baseline or >500 U/L (whichever comes first).

Abbreviations: ALT=alanine aminotransferase; INR=international normalized ratio; TBL=total bilirubin; ULN=upper limit of normal

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

a If multiple baseline ALT measurements are available, Baseline ALT will be defined as the average of the 2 most recent ALT measurements prior to first dose administered in parent study (ALN-AT3SC-001); if these two measurements differ by >50%, the average of the 3 most recent ALT measurements will be utilized (if available).

b In HCV RNA positive patients with elevated Baseline ALT whose ALT normalizes after successful DAA treatment (with SVR), Baseline ALT should be considered reset to the new normalized value and the stopping rules for HCV RNA negative patients with normal Baseline ALT should be applied going forward.

c Symptoms of liver injury (eg, nausea, right upper quadrant pain, jaundice).

d The frequency of laboratory monitoring should be decreased from biweekly to monthly once ALT has decreased to ≤1.5 × ULN or ≤1.5 × Baseline (whichever is higher).

e After dosing is held, once ALT has decreased to ≤1.5×ULN or ≤1.5×Baseline (whichever is higher), re-dosing may be considered. In patients with normal Baseline ALT, permanently discontinue dosing if ALT increases to >5×ULN following repeat dosing. In patients with elevated Baseline ALT, permanently discontinue dosing if ALT increases to >5×Baseline or >300 U/L (whichever comes first) following repeat dosing.

6.5.1.2 Non-invasive Assessments of Liver Stiffness in Patients with Hepatitis C Infection

In patients who are hepatitis C antibody positive, FibroScan (or FibroTest/aspartate aminotransferase to Platelet Ratio Index [APRI], if FibroScan is not available) will be assessed. If FibroScan, or FibroTest and APRI values indicate possible cirrhosis as defined by the criteria below, approval for continued dosing must be obtained following discussion with the study Medical Monitor and consideration of overall risk-benefit. Additional testing and evaluation may be required. Evidence of cirrhosis is defined according to one of the following assessments:

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

6.5.1.3 Antithrombin level criteria for a dose adjustment

With the introduction of the new dose and regimen with Protocol Amendment 07 following the global program dosing pause implemented by Sponsor in 2020, patients will receive fitusiran treatment according to the below antithrombin level scenarios and criteria. See the rationale for a new dosing justification in Section 1.5. Dose modification rules are detailed in the section below and displayed in Figure 1 and Figure 2.

A) Dose restart

a) Restart at 50 mg Q2M

- Patients that reach AT activity levels ≥22% (per central laboratory),
- Patients previously exposed to fitusiran at a dose of 50 mg QM or 80 mg QM with more than one AT activity level <15% (per central laboratory) at any time during fitusiran treatment,
- Patients will resume dosing at a dose of 50 mg Q2M and follow the modified IMP regimen SoAs (Table 3).

b) Restart at 50 mg QM or 80 mg QM (prior dose)

- Patients that reach AT activity levels ≥22% (per central laboratory),
- Patients previously exposed to fitusiran at a dose of 50 mg QM or 80 mg QM with no more than one AT activity level <15% (per central laboratory) at any time during fitusiran treatment (based on at least 3 months of prior AT measurements),
- Participant may have the option to remain on that dose and follow the SoAs in Table 1 and Table 2.

B) Dose escalation

a) Dose escalation to 50 mg QM

- After a period of dosing at 50 mg Q2M,
- Based on 2 steady state AT values >35% at the 50 mg Q2M dosing regimen,

- At least 2 of the 3 AT samples taken pre-dose at PR Month 4, PR Month 5 and PR Month 6 must be >35% to meet the escalation rule,
- Patients who previously had more than 1 AT value <15% at the 50 mg QM dose are not eligible to re-escalate to this dose level,
- If escalation rules are met, patient will receive the 50 mg dose at PR Month 7 (this will be considered the PR Month 1 of 50 mg QM, ie, the second 50 mg QM dose).

Note: If any of the doses prior to PR Month 6 are missed, then the decision-making for escalation must be shifted accordingly.

b) Dose escalation to 80 mg QM

- After a prior escalation to the 50 mg QM dosing regimen,
- Based on 2 steady state AT values >35% at the 50 mg QM dosing regimen,
- If a patient was dosed with fitusiran at PR Baseline and PR Month 1 visits, the AT values taken pre-dose at PR Month 2 and PR Month 3 of 50 mg QM will be used for assessment. If escalation rules are met, patient will receive the 80 mg dose at PR Month 4 (this will be considered the PR Day 1 of 80 mg QM),
- Patients who previously had more than 1 AT value <15% at the 80 mg QM dose are not eligible to re-escalate to this dose level,
- Patients on 50 mg QM prior to dosing pause are not eligible to escalate to 80 mg QM,
- If escalation rules are met, patient will receive the 80 mg dose at PR Month 4 (this will be considered the PR Day 1 of 80 mg QM).

Note: If any of the doses prior to PR Month 3 are missed, then the decision-making for escalation must be shifted accordingly.

c) In the rare circumstance that a patient does not meet criteria for escalation at this time the timepoints as described under sections a) and b) above and later meets criteria

- The investigator may use any of the central AT test results available once the patient is on steady state,
- The investigator will consult with the study Medical Monitor prior to any dose escalation.

C) Dose de-escalation

a) Patient receiving fitusiran at a dose of 50mg Q2M with more than 1 AT activity level <15% at any time on this dose and regimen

Patient must permanently discontinue fitusiran.

b) Patient having escalated to the 50 mg QM or 80 mg QM dose with now more than 1 AT activity level <15% after escalation.

In this unlikely circumstance, the Investigator will consult with the study Medical Monitor regarding further treatment with fitusiran, with the possibility of de-escalating the dose, if deemed beneficial for the study participant.

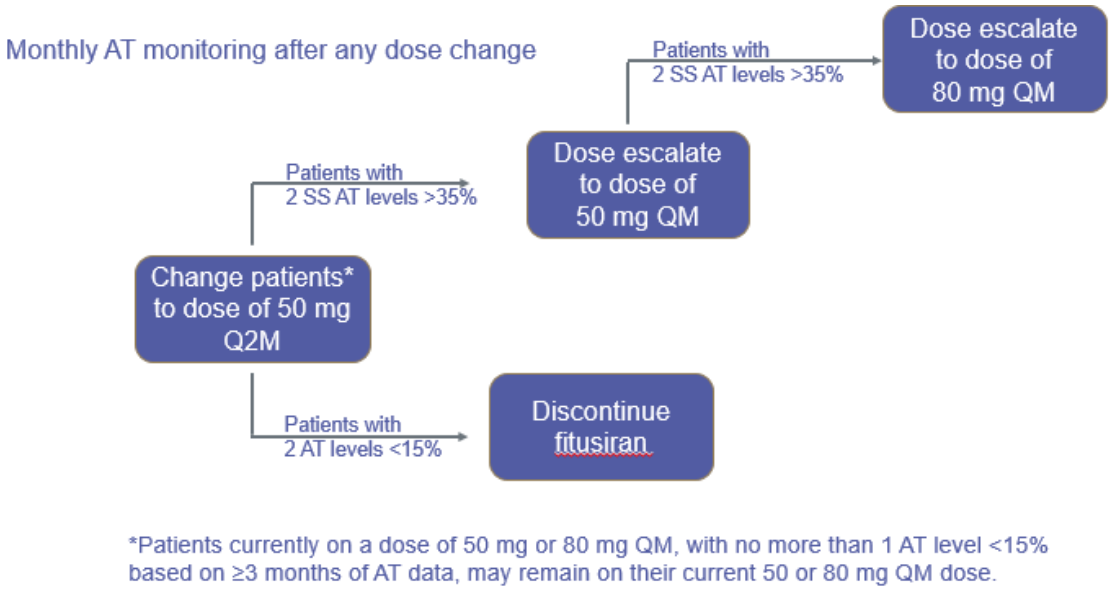
c) Patients having restarted at 50 mg QM or 80 mg QM dose subsequently having more than 1 AT activity level <15%.

Fitusiran dose must be reduced to 50 mg Q2M.

The first 50 mg dose should be administered no sooner than 2 months after the last 50 mg QM or 80 mg QM dose (the protocol-permitted visit windows are permissible) and only after the patients AT level reaches again at least 22 %.

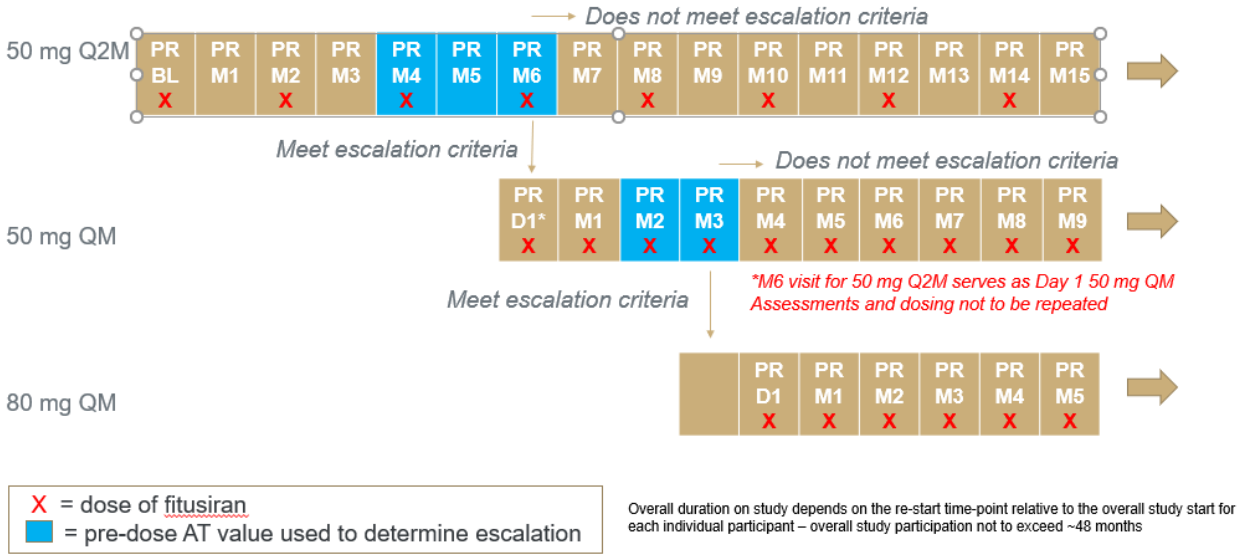
At each dose level, upon the first AT level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the results. If the result is <15%, this will be considered the second AT activity level <15%.

Figure 1 - Dose modification rules



Abbreviations: AT = antithrombin; QM = once monthly; Q2M = every second month; ss= steady state
Note: Restart following dosing pause to occur only once centrally measured AT activity levels ≥22%.

Figure 2 - Dose escalation process



Abbreviations: AT = antithrombin; BL = baseline; D = Day; M = Month; PR = post-restart; QM = once monthly; Q2M = every second month.
See rules and exceptions as described above in Section 6.5.1.3.

6.5.1.4 Temporary discontinuation due to a regional or national emergency

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 18.5). For all temporary intervention discontinuations, the associated reason/emergency should be recorded by the Investigator in the appropriate pages of the eCRF.

Re-initiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 4).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 18.5.

6.6 STUDY DRUG 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 clinic or as self-administered by the patient during the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

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

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

Any quality issue noticed with the receipt or use of an investigational medicinal product (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 9.2.11).

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

Under no circumstances will the Investigator supply IMP to a third party (except for Direct-to- Patient [DTP] shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.7 STUDY DRUG HANDLING AND DISPOSAL

All used, partially used, and unused vials or prefilled syringes of fitusiran will be returned to the Sponsor or its specified designee/depot or destroyed at the site according to applicable regulations.

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

7 PHARMACOKINETIC ASSESSMENTS

7.1 BLOOD AND SAMPLE COLLECTION

Blood and urine samples for PK analysis will be collected at the time points in the Schedule of Assessments (Table 1) and according to the detailed schedule presented in Appendix 18.1.

In a subset of patients who opt to participate, blood samples for PK analysis will be collected for additional time points as noted in the Schedule of Assessments (Table 1) and according to the detailed schedule presented in Appendix 18.1 (Table 13). In a separate subset of patients, pooled urine samples for PK analysis will be collected over 24 hours according to the time points presented in Appendix 18.1, (Table 14), as specified in the Schedule of Assessments (Table 1).

7.2 SAMPLE ANALYSIS

The concentration of fitusiran will be determined for each plasma sample using a validated assay. Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

7.3 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict patient response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by patients (see Section 13.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

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

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

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

All study patient data and samples will be coded such that no patient direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor

site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting patient confidentiality and personal data (see Section 18.3).

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

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

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

8 ASSESSMENT OF EFFICACY

8.1 ASSESSMENT OF BLEEDING EVENTS AND ADMINISTRATION OF FACTOR OR BYPASSING AGENT USAGE

Patients will be provided take home diaries. Patients will be trained to complete the diaries on an ongoing basis to record episodes of bleeding, administration of factor or BPA, as applicable, and response to factor or BPA treatment. Details will be recorded as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3). Data recorded in the diaries will be reviewed with the clinical study center staff or home healthcare professional.

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 episodes. Since bleeding episodes are recorded as an efficacy assessment of fitusiran, these will not be treated as AEs unless they meet any of the SAE criteria listed in Section 9.2.2.

The definition of bleeding episode types described below is based on consensus opinion of International Society on Thrombosis and Haemostasis (ISTH) as reflected in a recent publication (18).

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

Annualized bleeding rate (ABR) will be calculated as described in Section 10.2.3. Bleeding episodes will be managed according to Section 5.3.

8.2 PATIENT-REPORTED QUALITY OF LIFE

Quality of life will be assessed as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3) through the use of the EuroQoL (EQ-5D-5L) questionnaire, a standardized 5-question instrument for use as a measure of health outcomes (19), and the Haem-A-QoL (20), where available.

8.3 ASSESSMENT OF PLASMA ANTITHROMBIN ACTIVITY AND PLASMA THROMBIN GENERATION

Patients will have blood samples collected as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3) for the analysis of plasma AT activity and plasma TG. Analysis of plasma TG will be as determined by the calibrated automated thrombogram (CAT) assay. Antithrombin protein may be measured in a subset of plasma samples for correlation. Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

Data and biological samples will be stored and used for future research when consented to by patients (Section 7.3).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 18.5.

8.4 EXPLORATORY PERIOPERATIVE ASSESSMENTS OF SAFETY AND HEMOSTATIC EFFICACY IN PATIENTS UNDERGOING MAJOR OPERATIVE PROCEDURES

In patients undergoing elective or emergency major operative procedures during the study, safety and hemostatic efficacy assessments will be performed perioperatively according to the Schedule of Assessments outlined in Table 1, Table 2 and Table 3, 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 4): 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, prothrombin time (PT)/INR, fibrinogen, D-dimer); and hemostatic efficacy assessments (rating scale based on ISTH Scientific and Standardization Committee [SSC] definitions (18).

On day of the procedure and thereafter as specified in the Perioperative Schedule of Assessments (Table 4), the following may be assessed: coagulation parameters, TG, AT levels, factor VIII/IX levels, and hemostatic efficacy assessments.

Hemostatic response will be assessed at the end of the procedure (SDay 0), 24 hours postoperatively (SDay 1), and up to 14 days postoperatively (SDay 2-14; day to be determined by the Investigator) using the hemostatic efficacy rating scale (Table 17). A final postoperative visit will occur on SDay 28 (up to + 28 days) to document the date/time when perioperative hemostatic and thromboprophylaxis (if applicable) treatment was completed. The perioperative hemostatic rating will be collected via questionnaires that will be provided. The total number of patients in each rating category of hemostatic response ("none," "moderate," "good," and "excellent") will be summarized for both the intraoperative and postoperative assessments.

The end of the Perioperative Evaluation Period for each patient will be defined as the date/time when perioperative hemostatic treatment and thromboprophylaxis (if applicable) was completed, as documented at the last postoperative visit.

9 ASSESSMENT OF SAFETY

Safety assessments are performed according to the Schedule of Assessments (Table 1, Table 2 and Table 3). For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 18.5.

9.1 SAFETY PARAMETERS

9.1.1 Demographic and Medical History

Demographic data, medical history, and hemophilia history will be collected as specified in the Schedule of Assessments (Table 1).

Medical history and hemophilia history will only be collected for clinically relevant events occurring between the parent study and before administration of the first dose of study drug in this open-label extension study. Hemophilia history includes bleeding events and any treatment administered for bleeding events.

For all patients in this study, AEs from the parent study that are ongoing will be considered as part of the medical history.

9.1.2 Patient Education Module

Patients will be educated by Investigators or trained healthcare professionals on coagulation and general considerations with regards to managing hemophilia in the clinical setting of lowered-AT. This will be performed as specified in the Schedule of Assessments (Table 1 and Table 3).

9.1.3 Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3). When vital signs are scheduled at the same time as a physical examination or blood/urine sample collection, the vital signs must be performed first.

Vital signs will include systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature (oral, tympanic, or axillary), and will be measured in the seated or supine position using an automated instrument, or manually, after the patient has rested comfortably for 10 minutes. Temperature will be recorded in degrees Celsius. Heart rate will be counted for a full minute and recorded in beats per minute. Respirations will be counted for a full minute and recorded in breaths per minute.

For the safety of the patient, additional vital signs may be obtained at the discretion of the Investigator.

9.1.4 Weight and Height

Height will be measured only if it was not obtained in the parent study.

Body weight will be measured in kilograms (kg) as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3).

Body weight measurements to be used for the dose calculations will be collected during the clinical study center visit. Where doses are prepared in advance of the visit, the last recorded body weight may be used for dose calculation. If weight changes more than 10% at the predose assessment, the dose of study drug will be re calculated.

9.1.5 Physical Examination

A directed physical examination will be performed as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3). A directed physical examination 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. For patients undergoing a surgical procedure, a directed physical examination will also be performed as specified in the Perioperative Schedule of Assessments (Table 4).

9.1.6 Electrocardiogram

The 12-lead electrocardiogram (ECG) recordings will be obtained as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3). When an ECG is scheduled at the same time as a physical examination or blood/urine sample collection, the ECG must be performed first.

Standard 12-lead ECGs will be performed in the supine position after the patient has rested comfortably for 10 minutes. The parameters assessed will be rhythm, ventricular rate, PR interval, QRS duration, QT interval, and QTc (Bazett-corrected QT interval and Fridericia-corrected QT interval).

The Investigator or designee is responsible for reviewing the ECGs to assess whether the results are within normal limits and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. For any clinically significant abnormal results, the Investigator or designee must contact the CRO Medical Monitor to discuss continued participation of the patient in the study.

9.1.7 Laboratory Assessments

Where study assessments overlap with the parent study, the assessments only need to be performed once.

9.1.7.1 Hematology, Biochemistry, and Coagulation

Blood samples for the assessment of hematology, biochemistry, coagulation, and serology parameters will be collected as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3). Additional and repeat testing may be performed at the discretion of the Investigator.

The specific procedures for the clinical laboratory tests are provided in the Laboratory Manual.

Details regarding the processing, shipping, and analysis of the samples will also be provided in the Laboratory Manual.

Specific instructions for transaminase elevations are provided in Section 6.5.1.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 10 and will be assessed as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3).

While local laboratory results may be used for dosing decisions and urgent clinical decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 10 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 with available results, central laboratory results will be relied upon for clinical and dosing decisions.

Table 10: Clinical Laboratory Assessments

Hematology	
Complete blood count (CBC)[a]	Neutrophils, absolute and %
White blood cell (WBC) count	Lymphocytes, absolute and %
Red blood cell (RBC) count	Monocytes, absolute and %
Hemoglobin	Eosinophils, absolute and %
Hematocrit	Basophils, absolute and %
Mean corpuscular volume	Platelets[a]
Mean corpuscular hemoglobin	CD4 in HIV seropositive patients[a]
Mean corpuscular hemoglobin concentration	
Biochemistry	
Sodium	Alanine aminotransferase (ALT)
Potassium	Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)	Gamma glutamyl transferase (GGT)
Creatinine and eGFR (using the MDRD formula)	Total protein
Albumin	Uric acid
Calcium	Lactate dehydrogenase
Phosphate	Bilirubin (total and direct)
Glucose	Chloride
C-reactive protein (CRP)	Alkaline phosphatase (ALP)
Carbon dioxide	
Coagulation	
International normalized ratio (INR) Antithrombin (AT) activity[b]	FVIII for patients with hemophilia A (screening and perioperatively)
Thrombin generation (TG) by calibrated automated thrombogram (CAT) assay[b]	FIX for patients with hemophilia B (screening and perioperatively)
Prothrombin time (PT)	Activated partial thromboplastin time (APTT)
Fibrinogen	D-dimer Prothrombin fragment 1, 2
Hepatic Tests	
HAV antibody IgM and IgG	HCV antibody[c]
Hepatitis B surface antigen (HBsAg) Hepatitis B core antibody: IgM and IgG anti-HBc	HCV RNA PCR – qualitative and quantitative assays[c] HEV antibody IgM and IgG

a At Screening, only a complete blood count, platelet count, and CD4 in HIV seropositive patients is required (a CD4 result from the previous 6 months may be used to confirm eligibility).

b Plasma AT and TG by CAT are also listed under the efficacy assessments.

c In patients with a history of HCV infection, documentation detailing prior treatment prescribed for HCV infection will be collected. In addition, HCV genotyping will be performed in consented patients with positive HCV RNA.

Clinical laboratory assessments may be collected at the clinical site or at home by a trained healthcare professional. Central laboratory results are preferable. If not available, local laboratory results may be used.

Please see Section 6.5.1.1 for the LFT monitoring and dosing plan.

9.1.7.2 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.

For patients undergoing cholecystectomy due to cholecystitis, cholelithiasis or any other biliary pathology, the following should be performed, as possible: histopathological evaluation of the resected gallbladder and analyses of gallbladder contents including bile and gallstone composition. If performed, results should be included in the SAE and/or AESI report, as applicable.

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 6.5.1.1. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 11 will be performed, as well as hematology, biochemistry, LFT, and coagulation assessments from Table 10, AT levels, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring and dose modification will also be performed as outlined in Section 6.5.1.1.

Table 11: Hepatic Assessments in Patients who Experience LFT Elevations

Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Herpes Zoster Virus IgM, IgG
HIV 1 and 2[a]	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBsAg, 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

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

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

9.1.7.3 Urinalysis

Urine samples will be collected as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3) for evaluation of the following urinalysis parameters:

Table 12: Urinalysis Parameters

Urinalysis[a, b]	
Leukocytes	Red blood cells
Protein	pH (dipstick)
Bilirubin	Nitrite
Urobilinogen	Specific gravity
Ketone	Glucose

a Visual or automated inspection for appearance and color will occur.

b Urine microscopy will be performed if clinically indicated.

9.1.7.4 Antidrug Antibodies

To explore the effect of fitusiran on the induction of antidrug antibodies, blood samples will be collected as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3).

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

9.1.8 Inhibitor Status

Patients inhibitor status will be determined as specified in the Schedule of Assessments (Table 1, Table 2 and Table 3) by Nijmegen modified Bethesda assay.

9.1.9 FibroScan or FibroTest and APRI

FibroScan will be performed at the clinical study center according to the Schedule of Assessments (Table 1, Table 2 and Table 3) to determine cirrhosis status in patients with a history of hepatitis C. If FibroScan is unavailable, FibroTest and APRI will be performed at the central laboratory according to the Schedule of Assessments (Table 1, Table 2 and Table 3).

9.2 ADVERSE AND SERIOUS ADVERSE EVENTS

9.2.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Bleeding events will not be recorded as AEs but will be recorded on a separate bleeding events page of the eCRF. Data will be captured to classify whether bleeding events are related to hemophilia and whether they are spontaneous or traumatic.

Any medical condition that is present when a patient is screened and does not deteriorate should not be reported as an AE; however, if the medical condition does deteriorate at any time after administration of the first dose of study drug, it should be reported as an AE.

9.2.2 Serious Adverse Event Definition

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 inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- 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).

9.2.3 Eliciting Adverse Event Information

The patient should be asked about medically relevant changes in his health since the last visit. The patient should also be asked if he has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter).

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.

9.2.4 Adverse Event Reporting

The Investigator is responsible for reporting all AEs that are observed or reported from the first administration of study drug in this study, regardless of their relationship to study drug, through the follow-up visit.

All AEs must be fully 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 product, action taken, and outcome (including time and date of resolution, if applicable).

9.2.5 Assessment of Causality

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

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.

9.2.6 Assessment of Severity

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

Mild:	Mild events are those which are easily tolerated with no disruption of normal daily activity.
Moderate:	Moderate events are those which cause sufficient discomfort to interfere with normal daily activities.
Severe:	Severe events are those which incapacitate and prevent usual activity.

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).

9.2.7 Adverse Events of Special Interest

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

- ALT or AST elevations >3× ULN
- Suspected or confirmed thrombosis
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of fitusiran

- Systemic injection associated reactions (IARs), defined as hypersensitivity reactions which are related or possibly related to IMP.
- Cholecystitis*
- Cholelithiasis*

*See Section 9.1.7.2 for recommendations on additional evaluations to be performed for participants undergoing cholecystectomy.

9.2.7.1 Recording Adverse Events of Special Interest

For AEs that are considered AESI, additional clinical, laboratory, and diagnostic information may be collected based upon the severity or nature of the event.

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). 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.

If a patient has ISRs meeting any of the following criteria, the Investigator, or delegate, should contact the study Medical Monitor and submit a supplemental ISR eCRF:

- ISRs that are recurrent and/or demonstrate a pattern of increasing severity
- Any ISR that is determined to be severe and/or a cause for study drug discontinuation
- Any ISR that, in the opinion of the Investigator, requires further medical evaluation or treatment

In some cases, where it is medically appropriate, further evaluation may include photographs, referral to a dermatologist, skin biopsy, or other laboratory testing. If a biopsy is obtained, the Sponsor may request that the biopsy also be reviewed by a central dermatopathologist. To better understand the safety profile of the study drug, additional analysis of biopsy tissue may be performed according to local regulations.

For patients with hepatic AEs, local laboratory results may be collected to monitor LFT levels or other laboratory parameters.

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

9.2.8 Coding of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

9.2.9 Serious Adverse Event and Adverse Events of Special Interest Reporting

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 9.2.2 and any AESI must be reported to the CRO within 24 hours from the time that clinical study site personnel first learn of the event. All SAEs and AESI must be reported regardless of the relationship to study drug.

The initial report of SAEs 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 causality to study drug

To report the SAE or an AESI, complete the SAE/AESI form.

Within 24 hours of receipt of relevant follow-up information, the Investigator must update the SAE/AESI form. SAE/AESI forms must be reported using the contact information provided below.

SAE Reporting Contact Information
PSI CRO
SafetyDesk@psi-cro.com

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

9.2.9.1 Notifying the Institutional Review Board/Independent Ethics Committee

SAEs and/or 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.

9.2.9.2 Sponsor Reporting: Notifying Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency 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.

The following describes the safety reporting timeline requirements for suspected unexpected serious adverse reactions and other reportable events:

Immediately and within 7 calendar days:

- Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and fatal or life threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 15 calendar days:

- Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and serious, but not fatal or life threatening, and there is evidence to suggest a causal relationship between the study drug and the reaction.
- Any finding from tests in laboratory animals that: suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the trial subjects.

In addition, periodic safety reporting to regulatory authorities will be performed by the Sponsor, or its representative, according to national and local regulations.

9.2.9.3 Sponsor Notification of Participating Investigators

All Investigators will be informed by the Sponsor, or its representative, of relevant clinical safety findings from this or other clinical studies, as well as any new findings from tests in laboratory animals that significantly impact the benefit/risk to patients in this study. All reports should be transmitted to the IEC/IRB that approved the study.

9.2.10 Pregnancy Reporting

If the female partner of a patient becomes pregnant during the course of this study, the Investigator must report the pregnancy to the CRO within 24 hours of being notified of the pregnancy. The pregnancy should be followed by the Investigator until its conclusion.

9.2.11 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.

10 STATISTICS

A detailed Statistical Analysis Plan will be written after finalizing the protocol and before database lock. The plan will detail the implementation of all the statistical analyses in accordance with the principal features stated in the protocol.

10.1 NUMBER OF PATIENTS

Up to 48 patients with moderate or severe hemophilia A or B who have previously participated in a clinical study with fitusiran may be enrolled if they meet the eligibility criteria for this study. The size of this study is not determined via power analysis of particular hypotheses tests.

10.2 STATISTICAL METHODOLOGY

All study data will be presented in by-patient data listings. Statistical analyses will be primarily descriptive. Summary tables will be presented by starting dose level and final dose level/frequency of fitusiran separately for patients with and without inhibitors.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented.

All analyses will be conducted for patients with and without inhibitors separately.

10.2.1 Populations to be Analyzed

The following populations (ie, analysis sets) may be evaluated and used for presentation of the data:

- Safety Analysis Set: All patients who receive at least a partial dose of fitusiran will be included in the safety analyses.
- Per Protocol Set: All patients in the safety analysis set who have no major protocol violations.
- PK Analysis Set: All patients who receive at least 1 dose of study drug and have at least 1 blood sample collection postdose to determine plasma concentrations of fitusiran.
- PD Analysis Set: All patients who receive at least 1 dose of fitusiran and have at least 1 blood sample collection postdose to determine plasma AT and TG levels will be included in the PD analyses.

The Safety Analysis Set will be the primary set for safety assessments. Both the Safety Analysis Set and the Per Protocol Set will be used to assess efficacy endpoints. The PK Analysis Set will be used for PK analysis and the PD Analysis Set will be used for PD analyses. All the analysis

sets before and after the 2020 dose pause will be populated separately. Accordingly, the statistical analysis will be performed based on each analysis set respectively.

10.2.2 Baseline Evaluations

Demographic data will be summarized by dose level and overall.

Descriptive statistics will be provided for age, height, weight, and body mass index at screening. Frequencies and percentages will be tabulated for sex, race, and ethnicity.

10.2.3 Efficacy Analyses

Annualized bleed rate estimate will be calculated as the number of bleed events occurring 4 weeks after the first dose of fitusiran in this study and until the End of Study visit. Bleed-free duration will be defined as the maximum time intervals between 2 bleeding events and will be analyzed descriptively. Bleed rate reduction and percentage reduction compared with pretreatment will also be calculated.

A weight-adjusted consumption of FVIII or FIX or BPA will be assessed.

Patient-reported QoL will be assessed by descriptive statistics for the EQ-5D-5L questionnaire. Descriptive statistics will be provided for observed values and changes from baseline (ie, Day 1, predose in the current study).

10.2.4 Pharmacodynamic Analysis

The pharmacodynamic evaluation will include an analysis of plasma AT activity and protein level and TG (determined by CAT assay). Descriptive statistics will be presented by study day for actual results and change from baseline.

10.2.5 Exploratory Analyses

For patients who undergo major operative procedures during the study, the total number of patients in each rating category of hemostatic efficacy response (“none,” “moderate,” “good,” and “excellent”) will be summarized at each time point for both the intraoperative and postoperative assessments.

10.2.6 Safety Analyses

Adverse events will be summarized by the MedDRA System Organ Class and Preferred Term. Incidence of treatment-emergent adverse events (TEAEs; those events that started after exposure to study drug or worsened in severity after dosing) will be presented by dose level and overall. Incidence of TEAEs will also be presented by maximum severity and relationship to study medication or underlying hemophilia. The incidence of SAEs and AEs leading to discontinuation of treatment will also be tabulated. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory data (including biochemistry, hematology, urinalysis, and coagulation) and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation. Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or before Day 1. Abnormal physical examination findings, 12-lead ECG data, and antidrug antibody results will be presented in a by-patient data listing. Antidrug antibody results will also be tabulated.

10.2.7 Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using a population PK approach.

In addition to performing population PK, in a subset of patients, the following PK parameters will be evaluated using non-compartmental analysis: maximum plasma concentration (Cmax), time to maximum plasma concentration (tmax), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), apparent clearance (CL/F), and apparent volume of distribution (V/F). The amount of fitusiran or metabolite excreted in urine will also be estimated using non-compartmental analysis. Other parameters may be calculated, if deemed necessary.

10.2.8 Interim Analysis

Interim data examinations may be performed and will generally be descriptive in nature. As this is an open-label, extension study, interim analyses may be performed and will be described in the SAP.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1 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, International Council on Harmonisation (ICH) GCP, and all applicable regulatory requirements.

Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

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

11.2 AUDITS AND INSPECTIONS

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection by the Sponsor is to systematically and independently examine all study-related activities 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. The Investigator should contact the Sponsor, or its designee, immediately if contacted by a regulatory agency about an inspection.

11.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The PI must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Study personnel are expected to adhere to the following practices, governed by GCP and all applicable regulatory requirements. To ensure these practices are in place, the Sponsor may conduct a quality assurance audit.

The Investigator will submit reports of SAEs as outlined in this protocol. In addition, the Investigator agrees to submit progress reports to his/her IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Deviations from the protocol necessary to protect patient safety should be reported to the CRO within 24 hours of knowledge of the event.

Any communications from regulatory agencies in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the CRO.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol.

Regulatory authorities will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Study Report according to national and any local regulations.

13 ETHICS

13.1 ETHICS 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

13.2 ETHICAL CONDUCT OF THE STUDY

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

13.3 WRITTEN INFORMED CONSENT PROCESS

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

- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

14 DATA HANDLING AND RECORD KEEPING

- 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 electronic CRF 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.

14.1 INSPECTION OF RECORDS

The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

14.2 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 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 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.

15 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.

16 DISSEMINATION OF CLINICAL STUDY DATA

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

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

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

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18 APPENDICES

18.1 PHARMACOKINETIC ASSESSMENT TIME POINTS

Detailed collection of schedules for blood (Table 13) and urine (Table 14) samples for PK analysis are presented below.

Table 13: Pharmacokinetic Time Points

Study Day	Protocol Time (hh:mm)	PK Blood
Day 1, Month 12 (Day 361 ±7 days) and Month 24 (Day 721 ±7 days)[a]	Predose (within 60 minutes before dosing)	X
	00:30 (±2-min)	X
	02:00 (±5-min)	X
	04:00 (±30 min)	X
	08:00 (±30-min)	X
Day 2, Month 12 (Day 362 ±7 days) and Month 24 (Day 722 ±7 days)[a]	24:00 (±2 hours)	X

a Month 24 assessment to be performed in a subset of patients who opt to participate.

Table 14: Urine Pharmacokinetic Time Points

Study Day	Protocol Time (hh:mm), Pooled Urine
Month 24 (Day 721 ±7 days)	Postdose, 0:00 to 06:00 (±30 min)[a]
	06:00 (±30 min) to 12:00 (±30 min)
Month 24 (Day 721 to Day 722 ±7 days)	12:00 (±30 min) to 24:00 (±2 hours)

Note: To be performed in a subset of patients who opt to participate. Urine volume will be recorded for each urine collection interval.

a Patients must empty bladder before this urine collection interval.

Table 15: ADA timepoints in all patients at 50 mg Q2M dose

Study Day	Protocol Time (hh:mm)	ADA
Day of dose re-start	Predose (within 240 minutes before dosing)	X
PR Month 6	Predose (within 240 minutes before dosing)	X
PR Month 12	Predose (within 240 minutes before dosing)	X
PR Month 24	Predose (within 240 minutes before dosing)	X[a]
PR Month 36	Predose (within 240 minutes before dosing)	X[a]

a ADA samples collected at PR Months 24 and 36 will only be analyzed if the preceding sample was ADA positive.

Table 16: ADA timepoints with dose escalation to 50 mg QM or 80 mg QM

Study Day	Protocol Time (hh:mm)	ADA
Day of new dose	Predose (within 240 minutes before dosing)	X
PR Month 6	Predose (within 240 minutes before dosing)	X
PR Month 12	Predose (within 240 minutes before dosing)	X
PR Month 24	Predose (within 240 minutes before dosing)	X[a]
PR Month 36	Predose (within 240 minutes before dosing)	X[a]

a ADA samples collected at PR Months 24 and 36 will only be analyzed if the preceding sample was ADA positive.

18.2 PERIOPERATIVE SCHEDULE OF ASSESSMENTS

18.2.1 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 or any tooth implantation
- Operative alteration of normal anatomy
- Crossing of a mesenchymal barrier (eg, pleura, peritoneum, dura)

18.2.2 Perioperative Assessments of Safety and Hemostatic Efficacy in Patients Undergoing Major Operative Procedures

In patients who undergo a major operative procedure while on study, questionnaires will be provided to capture the exploratory perioperative assessments of hemostasis. The questionnaires may be completed by the dentist/surgeon/anesthesiologist involved in the procedure, or by the Investigator in consultation with the involved dentist/surgeon/anesthesiologist. The questionnaires include the Hemostatic Efficacy Rating Scale for Major Operative Procedures (Table 17), based on the ISTH SSC definitions (18).

Table 17: Hemostatic Efficacy Rating Scale for Major Operative Procedures

Excellent	Intra-operative and post-operative blood loss similar (approximately within 10%) to the non-hemophilic patient • No extra (unplanned) doses of FVIII/FIX/BPAs needed AND • Blood component transfusions required are similar to non-hemophilic patient
Good	Intra-operative and/or post-operative blood loss slightly increased over expectation for the non-hemophilic patient (approximately between 10-25% of expected), but the difference is not clinically significant • No extra (unplanned) doses of FVIII/FIX/BPAs needed AND • Blood component transfusions required are similar to the non-hemophilic patient
Moderate	Intra-operative and/or post-operative blood loss increased over expectation (approximately 25-50%) for the non-hemophilic patient and additional treatment is needed • Extra (unplanned) dose of FVIII/FIX/BPAs needed OR • Increased blood component (within 2-fold) of the anticipated transfusion
None	Significant intra-operative and/or post-operative blood loss that is substantially increased over expectation (approximately >50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia • Unexpected hypotension or unexpected transfer to intensive care unit (ICU) due to bleeding OR • Substantially increased blood component (approximately >2 fold) of the anticipated transfusion requirement

See Section 8.4 for further details regarding major operative procedures while on study. The Perioperative Schedule of Assessments in patients undergoing major operative procedures while on study is presented in Table 4.

18.3 DATA PROTECTION

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

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

Protection of patient data

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

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

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

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.

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

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

18.4 COUNTRY-SPECIFIC REQUIREMENTS

There were no country-specific requirements.

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

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

Clinical supplies and dosing

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

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

Operational measures

Contingency procedures for continuation of the study in the event of a regional or national emergency declared by a governmental agency are suggested below and in Section 4.4, Section 6.1, and Section 6.5.1.4. These procedures apply to an emergency that prevents access to the study site, to optimize the safety of the patients, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

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

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data. For any patients receiving fitusiran, factors and BPAs, Investigator and/or designee should contact the patient via regular phone calls at least every two weeks to oversee the tolerability of the drugs, to check for AEs, review the bleed management including bleeding episodes and patient diary. Depending on the delay of patient on-site visit, PRO collection may also be considered via remote visits.
- If onsite visits are not feasible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. If a visit cannot be completed in its entirety, at a minimum the site should maintain contact with patients every 2 weeks, to check for AEs, review the bleed management including bleeding episodes.
- Use of local laboratory may be allowed; Hematology, serum chemistry, coagulation, and liver function tests (which are due at certain visits and which cannot be frozen) should be prioritized for local lab testing by the study site for continued safety assessment.

Contingencies implemented due to emergency will be documented.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and administration of study intervention may be temporarily delayed (see also Section 6.5.1.4).

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

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

18.6 PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Protocol Synopsis.

18.6.1 Amended Protocol 01

Changes to eligibility criteria:

- Exclusion criterion #3, updated to permit enrollment of patients with inhibitors who have a medical history of previous thrombotic event related to permanent indwelling venous access

Other changes:

- Maximum sample size increased to N=48 and sites increased to 30
- Bleed management guidelines revised for patients without inhibitors and added for patients with inhibitors
- Patients may resume standard prophylaxis or on-demand dosing with Factor or BPA at Investigator discretion after dosing of ALN-AT3SC has been completed and AT levels begin returning to Screening levels
- Removal of contraception language
- Use of fixed dose, provided that dose is no greater on a weight basis than the highest dose determined previously in the parent study (ALN-AT3SC-001) to be safe and well tolerated
- Addition of the Haem-A-QoL to assess QoL
- Addition of text based on EC feedback
- Clarification of overlapping study assessments (vs parent study)

18.6.2 Amended Protocol 02

Changes to objectives:

- Exploratory objective added for assessment of safety and hemostatic efficacy rating for operative procedures conducted in patients while on study

Other changes:

- Study duration expanded by 2 years to 4 years total
- Text added to permit self-administration of study drug during non-quarterly visits from Month 3 forward
- Patient activity levels assessment removed
- Adverse Events of Clinical Interest section added
- Body temperature method revised to include all types (oral, tympanic, axillary)
- Other minor corrections

18.6.3 Amended Protocol 03

Primary changes:

- Text and table added for LFT monitoring in patients with elevated ALT
- Text added to permit direct-acting antiviral treatment for HCV infected patients
- FibroScan (FibroTest and APRI where FibroScan unavailable) added to assess liver fibrosis/cirrhosis in HCV infected patients; added in text and to Schedule of Assessments
- Clinical development status text updated
- Risk-benefit text updated
- New bleed management recommendations added to text and new tables added
- Surgery table and footnotes updated to align with Phase 3 studies
- Optional plasma PK visit and optional urine PK visit added at Month 24
- Schedule of Assessments reformatted and visits adjusted where necessary per above changes
- Other minor corrections applied

18.6.4 Amended Protocol 04

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 this study
- Additional safety measures were implemented to mitigate risk of thrombosis in the lowered-AT setting, including updating bleed management guidelines, adding recommendations for monitoring and management of thrombotic events, clarification of definitions for bleeding episodes, revised recommendations for management of sepsis, and adding additional exploratory laboratory assessments
- Frequency of visits increased in Schedule of Assessments from quarterly schedule in years 2 to 4, to a monthly schedule
- 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
- Revision of hepatic tests for hepatitis B
- 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 of monthly AT monitoring visits after the final dose of ALN-AT3SC until AT activity level returns to ~60%
- 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 TG and other coagulation parameters
- Other minor corrections applied

18.6.5 Amended Protocol 05

AMENDMENT 05 (31 May 2018)

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

OVERALL RATIONALE FOR THE AMENDMENT

Clinical development and commercialization of fitusiran were granted from Alnylam Pharmaceuticals, Inc. to Genzyme Corporation, a Sanofi Company that will be assuming responsibility of the current clinical program. Therefore, the Alnylam logo and reference to Alnylam within the confidentiality statement were deleted from the title page. Throughout all sections of the protocol including the page headers and appendices, Alnylam has been changed to "the Sponsor" or "Sanofi Genzyme" as appropriate. In addition to change in Sponsor name, address, and contact details were also updated. The Sanofi Genzyme study code (LTE14762) has been added. The Alnylam study drug code ALN-AT3SC has also been updated to the generic drug name fitusiran. Sections regarding 'Criteria for Study Termination', 'Study Drug Accountability', 'Guidelines for Reporting Product Complaints/Medical Device Incidents (Including Malfunctions)', 'Study Monitoring', 'Ethics', 'Data Handling and Record Keeping', 'Publication Policy', and 'Dissemination of Clinical Study Data' have been created or updated to reflect the Sanofi Genzyme environment.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout	Name of Sponsor changed from "Alnylam Pharmaceuticals, Inc." to "Genzyme Corporation"	Change of protocol Sponsor
Throughout	Name of Sponsor contact changed from "Pushkal Garg" to "Olivier Huynh-Ba"	Change of protocol Sponsor; contact details
Section 1.3 (only at first occurrence)	"Sanofi Genzyme LTE14762" added to the Study number "ALN-AT3SC-002"	Change of protocol Sponsor; Sanofi Genzyme study ID required for administrative purposes on first use
Throughout	Name of product "ALN-AT3SC" changed to "Fitusiran"	Change of protocol Sponsor; name of product updated
Title page	Disclaimer note text changed	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 3.6	Criteria for Study Termination language updated for clarity	Change of protocol Sponsor; text aligned with Sanofi 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
Throughout	"Investigational study drug" changed to "Investigational medicinal product"	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment

Section # and Name	Description of Change	Brief Rationale
Section 6.6	"Accountability" section updated with reporting procedure to follow with regards to any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.)	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 9.1.7.1 (Table 7)	Hepatitis B surface antibody (anti-HBs) deleted	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 9.2.7	Systemic injection associated reactions (IARs) added to the criteria of adverse events of special interest	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 9.2.9	Heading updated from "Serious Adverse Event Reporting" to "Serious Adverse Event and Adverse Events of Special Interest Reporting"	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 9.2.11	New Section 9.2.11 "Guidelines for Reporting Product Complaints/Medical Device Incidents (Including Malfunctions)" added with text	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 11.1	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 13.1	Ethics Review language updated for clarity	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 13.2	Ethical Conduct of the Study language updated to provide additional details	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 13.3	Written Informed Consent Process language updated to provide additional process details and clarity	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 14	Data Handling and Record Keeping language updated to provide additional details and clarify responsibilities	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 14.2	Retention of Records section heading and text updated to include additional details to ensure confidentiality of patient data and records	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 15	Publication Policy language updated to provide additional process details and some text moved into Section 16	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Section 16	New Section 16 "Dissemination of Clinical Study Data" added with text	Change of protocol Sponsor; text aligned with Sanofi Genzyme environment
Appendix 18	Appendix 18.3 - appendix for Country-Specific Requirements and Appendix 18.4- 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

18.6.6 Amended Protocol 06

AMENDMENT 06 (05 March 2019)

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

OVERALL RATIONALE FOR THE AMENDMENT

- Study extension beyond 48 months: The ALN-AT3SC-002 (LTE14762) is an open-label extension study of the long-term safety and efficacy of fitusiran in patients with hemophilia A or B, with or without inhibitory antibodies to factor VIII or factor IX. The primary objective of this study is the safety and tolerability assessed by incidence, severity, relatedness, and seriousness of adverse events, and laboratory assessments. This amendment, as study duration extension, will enable patients who have completed 48 months study participation to continue to be treated and evaluated for long-term safety and efficacy over 24 additional months or until fitusiran becomes commercially available, whichever occurs first.
- Prefilled syringe with safety system (PFS-S): Study drug may be provided in prefilled syringes either at the clinic (healthcare setting) or in a nonhealth care setting (home injection) in a subset of patients receiving 80 mg monthly dose of fitusiran. The patient will be trained on prefilled syringe self-administration. Patients who have missed more than 6 consecutive fitusiran dose for any reason should utilize the study drug provided as a vial and syringe for at least 3 injections prior to utilizing prefilled syringe.
- After at least a 2-year period of participation in the study, visits and assessments will be adjusted with reducing frequency of routine clinical hematology/biochemistry and urinary laboratory evaluations (but must be performed if clinically indicated), coagulation testing and exploratory biomarkers. The study duration of all patients has reached adequate follow-up to allow this adjustment. Based on gathered cumulative safety data during the study without any new safety concern or any new potential risk for fitusiran, the Sponsor determined that current visits and assessments frequency does not contribute additional information needed to evaluate patient's safety beyond 2 years. This justifies the proposed visits and routine assessments frequency adjustment and will also reduce patient burden without compromising safety monitoring.

Description of visits content and frequency with corresponding assessments during the extended period beyond 48 months are detailed in the amended protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Updated the Sponsor contact from "Olivier Huynh-ba" to "Salim Kichou".	• Administrative

Section # and Name	Description of Change	Brief Rationale
Protocol synopsis exploratory objectives Section 2.3	Deleted following exploratory objective: To investigate in vitro coagulation response to the reduction of AT levels.	• There is no longer a consideration that some of the exploratory assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments and related objectives
Protocol synopsis methodology	Following texts updated from: "Patients will visit the clinical study center for monthly assessments, including administration of study drug. Fitusiran dosing may occur at home in patients who are trained on self-administration. For all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. Safety and efficacy assessments will be performed at the clinical study center at each monthly visit and during an End of Treatment visit. Patients will return to the clinical study center for an End of Study visit 30 days after the last dose of study drug. Separately, follow-up visits to assess AT activity levels should occur at monthly intervals until AT activity level returns to approximately 60% (per the central laboratory), or per Investigator discretion in consultation with the study Medical Monitor.	• Study extension beyond 48 months. • There is no longer a consideration that some of the routine assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.

Pharmacokinetic assessments will be performed on Day 1, at the Month 12 visit, and at the Month 24 visit (in a subset of patients). Patients will also return to the clinical study center on Day 2 and the day after the Month 12 and Month 24 (in a subset of patients) visits for further PK sampling. Pooled urine collection will also occur at the Month 24 visit in a subset of patients.

In patients who present to the study site for management of bleeding symptoms, samples will be collected for exploratory coagulation biomarker assessment, including TG."

to

"Patients will visit the clinical study center monthly up to the end of Year 2 and then every 6 months up to the end of Year 6 for assessments including administration of study drug. Fitusiran dosing may occur at home in patients who are trained on self-administration. For up to 2 years, all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased to quarterly for patients who have negative hepatitis C antibody titers and meet the following criteria for quarterly predose LFT monitoring:

a) Did not have any ALT elevation >3× ULN persisting for ≥2 months at any time during the previous 12 months.

b) Did not have any fitusiran doses held due to LFT elevations during the study.

Safety and efficacy assessments will be performed at the clinical study center at each clinic visit and during an End of Treatment visit. Patients will return to the clinical study center for an End of Study visit 30 days after the last dose of study drug. Separately, follow-up visits to assess AT activity levels should occur at monthly intervals until AT activity level returns to approximately 60% (per the central laboratory), or per Investigator discretion in consultation with the study Medical Monitor. (Note: for patients who opt for the commercially available fitusiran, these follow-up visits to assess AT activity level are not required).

Pharmacokinetic assessments will be performed on Day 1, at the Month 12 visit, and at the Month 24 visit (in a subset of patients). Patients will also return to the clinical study center on Day 2 and the day after the Month 12 and Month 24 (in a subset of patients) visits for further PK sampling. Pooled urine collection will also occur at the Month 24 visit in a subset of patients."

Section # and Name	Description of Change	Brief Rationale
Protocol synopsis duration of treatment	Updated following texts from "It is anticipated that patients in this study will receive treatment with open-label fitusiran for approximately 4 years." to "It is anticipated that patients in this study will receive treatment with open-label fitusiran for approximately 6 years or until fitusiran becomes commercially available, whichever occurs first."	• Study extension beyond 48 months.
Protocol synopsis exploratory assessments	Deleted following exploratory assessments: modified (heparin) activated partial thromboplastin time, plasma clot lysis, whole blood clot formation as assessed by ROTEM® (where available), evaluation of TG in an ex vivo assay with factor/BPA-spiked samples.	• There is no longer a consideration that some of the exploratory assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.
Protocol synopsis statistical methods	Updated following texts from "Descriptive statistics will be provided for clinical efficacy and exploratory data" to "Descriptive statistics will be provided for clinical efficacy data." Updated following texts from "Annualized bleed rate, bleed rate reduction, and percentage reduction compared with pretreatment will be calculated. Descriptive statistics will be presented for the EQ-5D questionnaire, plasma AT activity, and TG." to "Annualized bleed rate, bleed rate reduction, and percentage reduction compared with pretreatment will be calculated. Descriptive statistics will be presented for the EQ-5D questionnaire, Haem-A-QoL, plasma AT activity, and TG."	• Due to updates in assessments.
Schedule of assessments	Table 1 updated to reflect extension of the study beyond 4 years and deleted following exploratory assessments with the update in related footnotes: modified (heparin) APTT sampling, plasma clot lysis, whole blood clot formation by ROTEM® (where available), and exploratory biochemistry sampling. Reduced the frequency of routine clinical hematology/biochemistry and urinary laboratory evaluations (but must be performed if clinically indicated), coagulation testing and exploratory biomarkers for Years 3 and 4. Newly added Table 2 for schedule of assessments for the Years 5 and 6.	• Study extension beyond 48 months. • There is no longer a consideration that some of the routine and exploratory assessments would yield critical results. Therefor it was decided to reduce the study burden by deleting these assessments. • The study duration of all patients has reached adequate follow-up to allow adjustment for visits and routine assessments. Based on gathered cumulative safety data during the study without any new safety concern or any new potential risk for fitusiran, the Sponsor determined that current visits and assessments frequency does not contribute additional information needed to evaluate patient's safety beyond 2 years. This justifies the proposed visits

Section # and Name	Description of Change	Brief Rationale
		and assessments frequency adjustment and will also reduce patient burden without compromising safety monitoring.
Table 3 bleeding episode assessments – unscheduled visit table	Table number updated from "Table 3" to "Table 4". Deleted exploratory coagulation assessment and related footnote.	• Study extension beyond 48 months. • There is no longer a consideration that some of the assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.
Throughout	Wherever applicable, added reference of schedule of assessments Table 2.	• Study extension beyond 48 months.
Section 1.4	Updated following texts from "This study will allow patients to receive treatment with fitusiran for approximately 4 years." to "This study will allow patients to receive treatment with fitusiran for approximately 6 years or until fitusiran becomes commercially available, whichever occurs first."	• Study extension beyond 48 months.
Section 3.1	Updated following texts from "For all fitusiran dosing, liver function test (LFT) results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. Safety and efficacy assessments will be performed at monthly visits and during an End of Treatment visit. Unscheduled visits for study assessments may occur if deemed necessary by the study personnel. In addition, patients who complete the study or discontinue treatment will continue to have safety assessments and AT activity levels monitored at monthly intervals following the final fitusiran dose until AT activity levels return to approximately 60% (per the central laboratory), or per Investigator discretion in consultation with the study Medical Monitor." to "For up to 2 years, all fitusiran dosing, liver function test (LFT) results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased to quarterly for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1. Safety and efficacy assessments will be performed at time points specified in Table 1 and Table 2. Unscheduled visits for study assessments may occur if deemed necessary by the study personnel. In addition, patients who complete the study or discontinue treatment will continue to have safety assessments and AT activity levels monitored at time points specified in Table 1 and Table 2 following the final fitusiran dose	• Study extension beyond 48 months. • There is no longer a consideration that some of the assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.

Section # and Name	Description of Change	Brief Rationale
	until AT activity levels return to approximately 60% (per the central laboratory), or per Investigator discretion in consultation with the study Medical Monitor (Note: for patients who opt for the commercially available fitusiran, these follow-up visits to assess AT activity level are not required)."	
Section 4.3	Updated following texts from "When a patient withdraws or is withdrawn from the study, an Early Termination visit should occur 30 days following the patient's last dose. Separately, follow-up visits to assess AT activity levels should occur at monthly intervals until AT activity level returns to approximately 60% (per the central laboratory). For patients who withdraw early, at least 2 attempts will be made to contact the patient to complete an Early Termination visit." to "When a patient withdraws or is withdrawn from the study, an Early Termination visit should occur 30 days following the patient's last dose. Separately, follow-up visits to assess AT activity levels should occur at monthly intervals until AT activity level returns to approximately 60% (per the central laboratory) (Note: for patients who opt for the commercially available fitusiran, these follow-up visits to assess AT activity level are not required). For patients who withdraw early, at least 2 attempts will be made to contact the patient to complete an Early Termination visit."	• Study extension beyond 48 months. • There is no longer a consideration that some of the assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.
Section 5.1	Dosage form updated from "Sterile solution packaged in 2-mL Type I glass vials" to "Sterile solution packaged in 2-mL Type I glass vials or prefilled syringes", and related following footnote added "Study drug may be provided in prefilled syringes either at the clinic (healthcare setting) or in a nonhealth care setting (home injection) in a subset of patients receiving 80 mg monthly dose of fitusiran. The patient will be trained on prefilled syringe self-administration. Patients who have missed more than 6 consecutive fitusiran dose for any reason should utilize the study drug provided as a vial and syringe for at least 3 injections prior to utilizing prefilled syringe."	• To allow use of prefilled syringes of fitusiran.
Section 5.3	Updated following texts from "The bleed management plan should be reviewed by the Investigator with the patient at each clinic visit (and via telephone contact every 2 weeks [±4 days] between clinic visits) and updated as necessary." to "The bleed management plan should be reviewed by the Investigator or designee with the patient at each dosing (and via telephone contact every 2 weeks [±4 days] between fitusiran dosing) and updated as necessary."	• Clarification due to change in the assessments.

Section # and Name	Description of Change	Brief Rationale
Section 6.1	Updated following texts from "Fitusiran Solution for Injection (SC use) will be supplied as a sterile solution in vials." to "Fitusiran Solution for Injection (SC use) will be supplied as a sterile solution in vials or prefilled syringes."	• To allow use of prefilled syringes of fitusiran.
Section 6.2	Updated following texts from "Study drug labels will include all appropriate local labeling requirements on the vials and external packaging." to "Study drug labels and external packaging will include all appropriate information as per local labeling requirements."	• Clarification.
Section 6.4	Added following text "Patients and/or caregivers may also prepare fitusiran doses after receiving proper instruction."	• Clarification.
Section 6.5	Updated following texts from "For all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose." to "For up to 2 years, all fitusiran dosing administered at the study center or at home, LFT results are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose. From Year 3 onwards, the frequency of predose LFT monitoring may be decreased to quarterly for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1." Added following texts: Pre-filled Syringe with Safety System: Study drug may be provided in prefilled syringes either at the clinic (healthcare setting) or in a nonhealth care setting (home injection) in a subset of patients receiving 80 mg monthly dose of fitusiran. The patient will be trained on prefilled syringe self-administration. The Investigator and/or delegated designee will complete a treatment process with the patient and/or patient's caregiver to prepare and administer the injection using the pre-filled syringe with safety system for monthly injections. The first injection is given by the Investigator and/or delegated designee while teaching patient and/or caregiver on how to perform the injection. The second injection is performed by patient or caregiver under the supervision of the Investigator and/or delegated designee. Once patient or caregiver has completed the required training and the Investigator and/or delegated designee approves, patient or caregiver may prepare and self-administer the subsequent injection at home. Patients who have missed more than 6 consecutive	• Study extension beyond 48 months. • There is no longer a consideration that some of the assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments. • To allow use of prefilled syringes of fitusiran.

Section # and Name	Description of Change	Brief Rationale
	fitusiran dose for any reason should utilize the study drug provided as a vial and syringe for at least 3 njections prior to utilizing prefilled syringe.	
Section 6.5.1.1	Modified first criteria from "LFT results are to be obtained…" to "For up to 2 years, LFT results are to be obtained…" Added following texts in the first criteria: From Year 3 onwards, the frequency of predose LFT monitoring may be decreased to quarterly for patients who have negative hepatitis C antibody titers and meet following specific criteria: a) Did not have any ALT elevation >3× ULN persisting for ≥2 months at any time during the previous 12 months. b) Did not have any fitusiran doses held due to LFT elevations during the study.	• Study extension beyond 48 months. • There is no longer a consideration that some of the assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.
Section 6.7	Updated following texts from "All used, partially used, and unused vials of fitusiran will be…" to "All used, partially used, and unused vials or prefilled syringes of fitusiran will be…".	• To allow use of prefilled syringes of fitusiran.
Section 8.3, Section 9.1.7.1 Section 9.1.7.4	Deleted following sentence: On dosing days, blood samples will be collected predose.	• Administrative change to clarify the process due to study extension beyond 48 months.
Section 8.4 Section 8.6 Section 8.7	Deleted these sections. Subsequent section numberings updated accordingly.	• There is no longer a consideration that some of the exploratory assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.
Section 9.1.3	Deleted following sentence: On dosing days, vital signs will be measured predose.	• Administrative change to clarify the process due to study extension beyond 48 months.
Section 9.1.7.1 Table 8 Clinical laboratory assessments	Deleted following exploratory parameters: modified (heparin) APTT, plasma clot lysis test, and whole blood clot formation by ROTEM® (where available).	• There is no longer a consideration that some of the exploratory assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.
Section 9.2.9	Updated following texts from "All SAEs must be reported regardless of the relationship to study drug. The initial report should include at least the following information: • Patient's study number • Description and date of onset of the event	• Administrative change to clarify the process

Section # and Name	Description of Change	Brief Rationale
	• Criterion for serious • Preliminary assignment of causality to study drug To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAE forms must be reported using the contact information provided below. to "All SAEs and AESI must be reported regardless of the relationship to study drug. The initial report of SAEs 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 causality to study drug To report the SAE or an AESI, complete the SAE/AESI form. Within 24 hours of receipt of relevant follow-up information, the Investigator must update the SAE/AESI form. SAE/AESI forms must be reported using the contact information provided below."	
Section 10.2.5	Deleted following texts: For exploratory parameters including plasma clot lysis, modified [heparin] APTT, and whole blood clot formation (ROTEM), descriptive statistics will be presented for each scheduled time point.	• There is no longer a consideration that some of the exploratory assessments would yield critical results. Therefore, it was decided to reduce the study burden by deleting these assessments.

18.6.7 Amended Protocol 07

AMENDMENT 07 (25 November 2020)

This amended protocol (amendment 07) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

- The main purpose of this amendment is to introduce a risk mitigation strategy for vascular thrombotic events in patients exposed to fitusiran. This strategy aims to decrease the level of antithrombin reduction via a change in the fitusiran dosing regimen. A Schedule of Assessments was added to accommodate the new dose regimen and to ensure optimal monitoring during the transition.

- Cholecystitis and symptomatic cholelithiasis are newly identified risks of fitusiran. As such, cholecystitis and cholelithiasis have been added to the protocol as adverse events of special interest (AESIs).
- The amendment also includes the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic. The guidance provides instruction on how to ensure continued dosing, monitor patients and perform assessments remotely when study patients are unable to travel to the site.
- Other minor editorial changes have been made to improve the clarity and readability of the protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis	The following sentence added "Study assessments will be performed as specified in the Schedule of Assessments for monthly dosing (Table 1, Table 2 and Table 3) or every other month dosing (Table 5).	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events, added to align with the new SOA.
Synopsis, Section 6.5 and 6.5.1.	The following sentence modified "From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and meet the following criteria for quarterly predose LFT monitoring:"	To optimize safety monitoring procedures and facilitate the process.
Synopsis	The following texts added " After any modification to the dosing regimen: a)Did not have any ALT elevation >3× ULN persisting for ≥2 months at any time during the first 12 months under this regimen; b)Must not have had any fitusiran doses held during the first 12 months under this regimen"	To optimize safety monitoring procedures and facilitate the process.
Synopsis	The following sentence added "Fitusiran will be administered as a 50 or 80 mg SC injection once monthly or every 2 months according to the dose selection rules in Section 6.5.1 and the SoAs in Table 1, Table 2 and Table 3."	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events, added to align with the new SOA.
Synopsis	Statistical methods updated: "Results will be presented in summary tables by starting dose level." changed to "Results will be presented in summary tables by starting regimen and then by final dose regimen of fitusiran separately for patients with and without inhibitors.".	To add statistical analysis by final dose level/frequency to accommodate the new dose regimen,
List of Abbreviations and Definitions of Terms	New abbreviations added "Coronavirus Disease-19 (COVID-19), every 2 months (Q2M), every month (QM), reverse transcription-polymerase chain reaction (RT-PCR) and sever	To clarify.

Section # and Name	Description of Change	Brief Rationale
	acute respiratory syndrome coronavirus 2 (SARS-CoV-2)"	
	"duties and taxes paid" changed to "Direct-to-Patient".	To correct typo.
Table 1	Plasma AT activity to be assessed at M42.	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.
Table 1	Plasma TG to be assessed at M42.	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.
Table 1, Table 2	Table updated with COVID-19 Testing to be done at any time during the study.	To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic.
Table 1, Section 3.1	Foot note "b" modified "From Year 3 onwards, the frequency of predose LFT monitoring may be decreased for patients who have negative hepatitis C antibody titers and meet specific criteria defined in Section 6.5.1.1."	To optimize safety monitoring procedures and facilitate the process.
Table 1	Foot note "d": "Vital signs will be measured in the position after the patient has rested comfortably for 10 minutes." changed to "Vital signs will be measured in the seated or supine position after the patient has rested comfortably for 10 minutes."	To clarify.
Table 1	Foot note "k" added: "When patients reinitiate the study at their monthly dose (no dose change) they will have their AT, TG, and coagulation measured monthly for 6 months."	For clarity as the dosing regimen changed.
Table 2	Foot note "k" added: "When patients reinitiate the study at their 80mg or 50 mg monthly dose (no dose change) they will have their AT and TG measured monthly for 6 months."	For clarity as the dosing regimen changed.
Table 1, Table 2	Foot note "t" in Table 1 and "o" in Table 2 added respectively: "All study patients that are consenting to this procedure are requested to undergo testing for SARS-CoV-2 (virus responsible for COVID-19), which should include both RT-PCR and antibody testing. These tests should be performed as early as possible during the study. Alternatively, historical test results may be provided under certain circumstances as defined by Sponsor"	To clarify COVID-19 test.
Schedule of assessment, Table 3	New table "Modified IMP Regimen Schedule of Assessments (Year 1, 2, 3)" added as Table 3. Therefore, numerical order of all tables throughout document updated accordingly.	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.

Section # and Name	Description of Change	Brief Rationale
Section 6.6	"duties and taxes paid" changed to "Direct-to-Patient".	Typo.
Section 1.1	"The development of inhibitors is considered the most serious complication today and occurs in up to 30% of persons with severe hemophilia A, and 3-5% of persons with severe hemophilia B.[3] " updated to " Development of inhibitors to infused factor occurs mainly in severe hemophilia, and more frequently in hemophilia A (up to 39% of patients), than in hemophilia B (1% to 3.5% of patients).".	Reference updated.
Section 1.3	Paragraphs 1 to 3 removed. Added "The Investigator must become familiar with all sections of the fitusiran Investigator's Brochure which will be provided by the Sponsor before the start of the study and during the study, as amendments are completed.".	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.
Section 1.3.1	Paragraphs 1 to 3 removed. Added "Phase 1/2 clinical trials, monthly dosing with fitusiran in patients with hemophilia A and B, with or without inhibitors resulted in sustained antithrombin lowering and improved hemostasis as measured by reductions in patients' annualized bleeding rate (ABR)(13)(14).."	Refer to the IB for current updates.
Section 1.3.2	[redacted]	Refer to the IB for current updates.
Section 1.5	Dose rationale text updated.	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.
Section 1.6	Benefit-risk assessment text updated.	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.
Section 3.5	The following sentence added "Dose adjustment criteria are detailed in Section 6.5.1".	To align with instructions for AT-driven fitusiran regimen modification

Section # and Name	Description of Change	Brief Rationale
Section 3.5	The following sentence added: "Instructions for AT-driven fitusiran regimen modification are provided in Section 6.5.1.3."	To align with the new fitusiran dosing regimen.
Section 4.3	Adapted the section title to from "Withdrawal criteria" to "Discontinuation of the study intervention and patient discontinuation /withdrawal)	To address and clarify the criteria for study intervention and patient withdrawal, separately.
Section 4.3.1	Added "More than 1 AT measurements <15% if at a dose of 50 mg Q2M" as bullet points.	Risk mitigation measure for vascular thrombotic events.
Section 4.4	New section added.	To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic.
Section 5.3	"After initiating therapy with fitusiran, patients should call the Investigator prior to…" changed to "After initiating therapy with fitusiran, it is recommended patients call the Investigator prior to…"	For clarity.
Section 5.5	Monitoring and management of thrombotic events text updated.	Risk mitigation measure for vascular thrombotic events.
Section 5.7	"surgery" rephrased to major surgery"	For clarity
Section 6.1	The following paragraph added "The IMP may be supplied at the site or from the PI/site/Sponsor to the patient via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the patient. For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 18.6."	To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic.
Section 6.4	The following sentence removed "The study drug will be prepared using aseptic technique."	Administrative change to facilitate and clarify the process.
Section 6.5	The following sentence removed "Additional details can be found in the study operations manual."	Study operations manual not applicable for the study.
Section 6.5	"…in a subset of patients receiving 80 mg monthly dose of fitusiran." changed to "in a subset of patients receiving 80 mg SC injection once monthly".	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.
Section 6.5.1.1	The following paragraph added "Note: negative Hep C patients include patients who never met HCV, i.e., antibodies are negative, but also those with only positive antibodies without any viral load detected (i.e., patient has cleared the infection, but antibodies still detected as positive). To	For clarity.

Section # and Name	Description of Change	Brief Rationale
	confirm this eligibility, patients who cleared Hep C infection must have documented sustained negative virologic load.	
	2. After any modification to the dosing regimen: c) Did not have any ALT elevation >3× ULN persisting for ⩾2 months at any time during the first 12 months under this regimen d) Must not have had any fitusiran doses held during the first 12 months under this regimen".	
Section 6.5.1.3	New section added "Antithrombin level criteria for a dose adjustment"	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events.
Section 6.5.1.4	New section added "Temporary discontinuation due to a regional or national emergency"	To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic.
Section 7.3	New section added "Use of biological samples and data for future research"	To include biological sample and data use guidance to optimize operative process.
Section 8.3	Added following text "Data and biological samples will be stored and used for future research when consented to by participants (Section 7.3)."	To clarify operation process and follow guidance.
Section 8.3	The following paragraph added "For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 18.6."	To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic.
Section 9	The following paragraph added "Safety assessments are performed according to the Schedule of Assessments (Table 1, Table 2 and Table 3). For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 18.6."	To include the addition of new guidance to facilitate the continuation of the study in the event of a regional or national government declared emergency such as the COVID-19 pandemic.
Section 9.2.7	ASEI: Cholecystitis and Cholelithiasis added.	To reflect the updates of fitusiran safety profile and to optimize the monitoring process.
Section 9.2.7.1	The following paragraph added "For all ISRs, the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (e.g., descriptions, onset and resolution date, severity, treatment given, event outcome). A systemic reaction which includes the injection site, e.g., generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site, is not considered an ISR.".	For clarity.
Section 9.2.9	"Country-specific fax numbers will be included in the Study Operations Manual." removed.	Study operations manual not applicable for the study.

Section # and Name	Description of Change	Brief Rationale
Section 10.2	"Results will be presented in summary tables by starting dose level." changed to "Summary tables will be presented by starting dose level and final dose level/frequency of fitusiran separately for patients with and without inhibitors.".	To add statistical analysis by final dose level/frequency to accommodate the new dose regimen,
Section 11.1	The following paragraph added: "Monitoring details describing strategy methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents."	To include proactive monitoring details.
Section 11.1	"…must be retained by the Investigator for 15 years after study completion" changed to "must be retained by the Investigator for 25 years after study completion".	To align with the updated requirement.
Section 14	"The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents." changed to "The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (including remote access, if possible and authorized).".	For clarity.
Section 18.1	New tables added "ADA timepoints in all patients at 50 mg Q2M dose" and "ADA timepoints with dose escalation to 50 mg QM or 80 mg QM".	Fitusiran dosing regimen changed as a risk mitigation measure for vascular thrombotic events. ADA timepoints added to accommodate the new dosing regimen.
Section 18.3	New section added "Data protection".	To harmonize the content of protocol template updates and clarify operational process
Section 18.5.6	New section added "Amended Protocol 06"	To document protocol amendments history
Section 18.6	New section added "Contingency measures for a regional or national emergency that is declared by a governmental agency". .	To clarify contingency measures for a regional or national emergency such the COVID-19 pandemic.
Throughout	Minor editorial, typo error corrections and document formatting revisions	Minor, therefore, have not been summarized
Throughout	"CRF/eCRF" changed to "eCRF"	CRF not applicable for the study

18.6.8 Amended Protocol 08

Amendment 08 (08 December 2020)

This amended protocol 08 (amendment 08) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

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

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis		
Tables 1-3	Sentence added to footnotes "k": Upon the first AT activity level <15%, the patients must have another AT activity level sample drawn within 1 week of site receipt of the results.	To mandate a second AT activity level within 1 week of site receipt of an initial AT level result <15%.
Tables 1 and 2	Footnote added: This schedule applies for patients who continue to receive fitusiran under the 50 or 80 mg monthly dose without meeting criteria for adjusted dosing.	To clarify which Schedule of Assessments patients should follow if they continue on the fitusiran 80 mg or 50 mg monthly dose.
Table 3	Foot note "b" added following sentence "Patients will follow either the Q2M or QM dosing regimen according to the dose adjustment rules; see Section 6.5.1.3." Foot note "k" added the following sentence: "ADA samples will be collected within 240 minutes before dosing according to the schedule in Table 15 and Table 16."	For clarity.
Section 1.5	Updated the following text "If a patient has 2 steady state AT levels above 35%, the patient will be dose escalated to fitusiran 50 mg monthly." to "If a patient receiving fitusiran 50 mg once every 2 months has 2 steady state AT levels above 35%, the patient will be dose escalated to fitusiran 50 mg monthly. "	For clarity.
Section 6.5.1.3	Qualifier added to the bullet "after 50 mg Q2M:": Patients who previously had more than 1 AT level <15% at the 50 mg QM dose are not eligible to re-escalate to this dose level. Qualifier added to the bullet "after 50 mg QM:": Patients who previously had more than 1 AT level <15% at the 80 mg QM dose are not eligible to re-escalate to this dose level.	To specify and address dose adjustment based on AT activity levels.

Section # and Name	Description of Change	Brief Rationale
	The following text was inserted prior "Patients receiving fitusiran at a dose of 50 mg Q2M with more than 1 AT activity measurement <15% at any time on this dose during the study must permanently discontinue fitusiran.": At each dose level, upon the first AT level <15%, the patient must have another AT activity level sample drawn within 1 week of site receipt of the result. If this result is <15%, this will be considered the second AT activity level <15%.	
Section 18.5.7	New section added "Amended Protocol 07".	To document protocol amendments' history.
Throughout	Minor editorial, typo error corrections and document formatting revisions.	Minor, therefore, have not been summarized.

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