STATISTICAL ANALYSIS PLAN

An open-label extension study of subcutaneously administered fitusiran (formerly ALN-AT3SC) in patients with moderate or severe hemophilia A or B who have participated in a previous clinical study with fitusiran

Protocol Number:	LTE14762 (formerly ALN-AT3SC-002)
Protocol Version(s) and Date(s):	
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
Name of Test Drug:	SAR439774 (formerly ALN-AT3SC) (fitusiran)
Phase:	Phase 1/2
Sponsor:	Genzyme Corporation 50 Binney Street Cambridge, MA 02142, USA
Analysis Plan Version and Date:	1: 20 June 2018 2: 22 November 2019 3: 16 March 2023

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN **1**

TABLE OF CONTENTS **2**

ABBREVIATIONS **5**

1 INTRODUCTION **6**

2 STUDY OVERVIEW **7**

2.1 SYNOPSIS OF STUDY DESIGN 7

2.2 RANDOMIZATION METHODOLOGY 8

2.3 UNBLINDING 8

2.4 STUDY PROCEDURES 8

2.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL 8

2.6 OTHER MODIFICATIONS MADE TO THE STATISTICAL ANALYSIS PLAN 14

2.7 MODIFICATION MADE IN SAP TO THE STATISTICAL SECTION IN PROTOCOL 15

3 OBJECTIVES AND ENDPOINTS **16**

3.1 OBJECTIVES 16

3.1.1 Primary objective 16

3.1.2 Secondary objectives 16

3.1.3 Exploratory objectives 16

3.2 ENDPOINTS 16

3.2.1 Efficacy endpoints 16

3.2.2 Pharmacokinetic endpoints 16

3.2.3 Pharmacodynamic endpoints 17

3.2.4 Safety variables 17

3.2.5 Antidrug antibody endpoints 17

4 PARTICIPANT POPULATION **18**

5 GENERAL STATISTICAL METHODS **20**

5.1 SAMPLE SIZE JUSTIFICATION 20

5.2 GENERAL METHODS 20

5.3 COMPUTING ENVIRONMENT 22

5.4 TIMING OF ANALYSES 22
5.5 BASELINE DEFINITIONS 22
5.6 RANDOMIZATION STRATIFICATION FACTORS 23
5.7 MULTIPLE COMPARISONS/MULTIPLICITY 23
5.8 MISSING DATA 23
5.9 PROTOCOL DEVIATIONS 23
5.10 DERIVED ANALYSIS VISIT WINDOWS 23
6 STATISTICAL ANALYSES 26
6.1 PARTICIPANT DISPOSITION 26
6.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS 26
6.3 EFFICACY 26
6.3.1 Analysis of long-term durability and efficacy 29
6.3.1.1 Annualized bleeding rate 29
6.3.1.2 Bleed-free duration 29
6.3.2 Quality of life 30
6.3.2.1 EQ-5D-5L 30
6.3.2.2 Haem-A-Qol 30
6.3.3 Annualized weight-adjusted consumption of BPA and factor 30
6.4 PHARMACODYNAMIC ANALYSIS 30
6.4.1 AT lowering and peak thrombin 31
6.5 ANALYSES DURING DOSE INTERRUPTION 31
6.6 ADDITIONAL EXPLORATORY ANALYSES 32
6.7 PHARMACOKINETIC ANALYSIS 32
6.8 SAFETY ANALYSES 32
6.8.1 Study drug exposure 33
6.8.2 Adverse events 33
6.8.3 Laboratory data 35
6.8.4 Vital signs and physical examination 37
6.8.5 Electrocardiogram 37
6.8.6 Medical history 37
6.8.7 Concomitant medications 37
6.8.8 Bleed management guidelines 38

6.9 ANTIDRUG ANTIBODY 38
6.10 PRE-FILLED SYRINGE 38
6.11 SUBGROUP ANALYSIS 38
7 REFERENCES 39
8 APPENDIX: QUESTIONNAIRE/SCORING 40
8.1 HAEM-A-QOL 40
8.2 EUROQOL-5 DIMENSION 5 LEVEL (EQ-5D-5L) SCORE 41

ABBREVIATIONS

Abbreviation	Definition
ABR	annualized bleeding rate
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AT	antithrombin
AUC	area under the concentration-time curve
BFD	bleed-free duration
BMI	body mass index
BPA	bypassing agents
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CSR	clinical study report
EQ-5D-5L	Euro Quality of Life- 5 dimensions 5 levels
FIX	factor IX
FVIII	factor VIII
GalNAc	N-acetylgalactosamine
HGLT	Higher level group term
MD	multiple-dose
MAD	multiple-ascending dose
OLE	open-label extension
PK	pharmacokinetic
Q1	first quartile
Q3	third quartile
QoL	quality of life
QTcF	Fridericia's corrected QT
SAD	single-ascending dose
SAP	statistical analysis plan
SEM	standard error of the mean
SI	international system of units
siRNA	small interfering ribonucleic acid
SOC	system organ class
$t_{½\beta}$	elimination half-life
TG	thrombin generation
t_{max}	time to maximum plasma concentration
VAS	visual analogue scale
V/F	volume of distribution

1 INTRODUCTION

Hemophilia A and hemophilia B are X-linked recessive inherited bleeding disorders, characterized by deficiency of coagulation factor VIII (FVII) or factor IX (FXI), leading to a profound defect in thrombin generation with impaired hemostasis and increased risk of bleeding. Antithrombin (AT) is a liver-expressed natural anticoagulant that plays a key role in inhibiting thrombin. Extensive preclinical in vitro and in vivo studies have described reduction of AT as a potential safe and effective way to correct thrombin generation in both hemophilia A and B and control against microvascular and macrovascular bleeding episodes. Therefore, suppression of AT production is being investigated as a potential hemophilia treatment.

Fitusiran (SAR439774 [formerly Alnylam ALN-AT3SC]) is an investigational agent, comprising a synthetic small interfering RNA (siRNA) covalently linked to a triantennary GalNAc ligand, designed to suppress liver production of AT as a strategy to rebalance the hemostatic system, thereby improving thrombin generation and hemostasis in individuals with hemophilia.
A fixed-dose subcutaneous therapy that can effectively and safely prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B, may reduce treatment burden, improve clinical outcomes and enhance quality of life.

This statistical analysis plan (SAP) provides a comprehensive description of statistical analyses to be implemented to assess the clinical safety and efficacy of Study LTE14762(formerly ALN-AT3SC-002) protocol amendment 9 dated 23 June 2021. The data analyses will be used for the clinical study report (CSR).

2 STUDY OVERVIEW

2.1 SYNOPSIS OF STUDY DESIGN

LTE14762 is an open-label extension (OLE) study to evaluate long-term safety, tolerability, and efficacy of subcutaneously administered fitusiran in patients with moderate or severe hemophilia A or B, with or without inhibitory antibodies to factor VIII or factor IX, who previously tolerated dosing in the parent study, TDR14767(formerly ALN-AT3SC-001). The primary objective of this study is to evaluate the long-term safety and tolerability of fitusiran, assessed by incidence, severity, relatedness, and seriousness of adverse events, and laboratory assessments.

TDR14767(ALN-AT3SC-001) was a Phase 1 study that evaluated the safety, tolerability, and PK of fitusiran in healthy male volunteers and male patients with hemophilia A or B. TDR14767(ALN-AT3SC-001) was conducted in 4 parts:

Part A: a randomized, placebo-controlled, single-blind single-ascending dose (SAD) phase in healthy subjects

Part B: an open-label, multiple-ascending dose (MAD) phase in patients with moderate to severe hemophilia A or B without inhibitors

Part C: an open-label, exploratory multiple dose (MD) phase in patients with moderate to severe hemophilia A or B without inhibitors

Part D, an open-label MD phase in patients with moderate to severe hemophilia A or B with inhibitors.

Study TDR14767(ALN-AT3SC-001) was completed on 20 July 2017 (last patient last visit).

Patients who received all 3 doses of study drug in TDR14767(ALN-AT3SC-001) and completed required study visits in the parent study were eligible for participation in LTE14762. All enrolled participants will initially receive a 50 mg or 80 mg dose of fitusiran once monthly.

A change in the fitusiran dosing regimen(referred as ‘revised dose and regimen’ throughout this SAP) 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. Detailed dosing adjustment plan can be found in Protocol Amendment 09 section 6.5.1.3.

2.2 RANDOMIZATION METHODOLOGY

Not applicable.

2.3 UNBLINDING

Not applicable.

2.4 STUDY PROCEDURES

The schedule of assessments is described in the study protocol (Table 1 for Years 1 to 4, Table 2 for Years 5,6, and 7 and Table 3 for Modified IMP Regimen Schedule of Assessments).

2.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section. The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the protocol statistical section.

The first patient was enrolled on 08-Oct-2015.

Table 1 - Protocol amendment statistical changes

Amendment number	Date approved	Rationale	Description of statistical changes
5	31-May-2018	"Adverse events of clinical interest" changed to "Adverse events of special interest; and Systemic injection associated reactions (IARs) added to the criteria of adverse events of special interest (to align text with Sanofi Genzyme environment).	AESI (instead of AECI) will be listed and summarized as per Section 6.8.2 of this SAP.
6	05-Mar-2019	Deleted following exploratory objectives: i) To investigate in vitro coagulation response to the reduction of AT levels. ii) Modified (heparin) activated partial thromboplastin time, iii) Plasma clot lysis, iv) Whole blood clot formation as assessed by ROTEM®, v) Evaluation of TG in an ex vivo assay with factor/BPA-spiked samples.	Deleted these assessments and related objectives from Sections 3.1.3 and 6.6 of the SAP.

Amendment number	Date approved	Rationale	Description of statistical changes
7	25-Nov-2020	To introduce a risk mitigation strategy for vascular thrombotic events in patients exposed to fitusiran 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.	Added revised dose and regimen Added AESI: Cholecystitis and Cholelithiasis Allowed COVID19 test for analysis
8	08-Dec-2020	To minimize the time between 2 antithrombin (AT) measurements if the first AT result is <15%.	NA
9	23-Jun-2021	Administrative change	Added NCT number and updated amended protocol version to 9.0
9	23-Jun-2021	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.	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).”
9	23-Jun-2021	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.	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.”
9	23-Jun-2021	To accommodate the extension of study duration for few patients following the introduction of revised dose and regimen.	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.
9	23-Jun-2021	To correct an omission.	Added Coagulation assessment in EOS/ET visit.

Amendment number	Date approved	Rationale	Description of statistical changes
9	23-Jun-2021	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.	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."
9	23-Jun-2021	To align with eCRF.	Introduced a new row for "Hemostatic/Thromboprophylaxis Treatment Plan."
9	23-Jun-2021	For clarity.	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.
9	23-Jun-2021	For clarity.	Added "up to 28 days" following "SDay 28" in the column for postoperative Visit 3.
9	23-Jun-2021	For clarity and facilitate trial operational practice.	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 Day 28 visit is not required."

Amendment number	Date approved	Rationale	Description of statistical changes
9	23-Jun-2021	To update fitusiran efficacy data.	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.”
9	23-Jun-2021	To align with the fitusiran safety updates.	[redacted]
9	23-Jun-2021	To align with the fitusiran safety updates.	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.”
9	23-Jun-2021	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.	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.”
9	23-Jun-2021	For clarity.	Specified in “Protocol Amendment 07” that introduced the fitusiran revised dose and regimen.
9	23-Jun-2021	To reflect the fitusiran revised dose and regimen.	Revised the language of patients on fitusiran dose “on that dose” to “on either dose, respectively.”
9	23-Jun-2021	For clarity.	Updated “pharmacokinetic/pharmacodynamic (PK/PD) model” with “population pharmacokinetic/pharmacodynamic (pop PK/PD) model.”
9	23-Jun-2021	To consider the context of fitusiran on pause.	Updated the text on LFT monitoring by including “and provides instruction for the potential discontinuation of fitusiran.”
9	23-Jun-2021	To clarify that the use of emicizumab (Hemlibra®) during the study is prohibited.	Included the following text “Use of emicizumab (Hemlibra®) during the study is not permitted.“
9	23-Jun-2021	To consider the context of fitusiran on pause.	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.”

Amendment number	Date approved	Rationale	Description of statistical changes
9	23-Jun-2021	For clarity regarding the use of factor concentrates or BPAs.	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.”
9	23-Jun-2021	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.	Introduced a new section on alcohol restrictions as Section 5.11.
		To classify AT utilized for AT reversal as NIMP.	Defined antithrombin (AT) utilized for AT reversal as NIMPs and clarified IMP/NIMP accountability.
		To adapt to fitusiran new dose and regimen.	Removal of fitusiran dosing frequency of "once every month".
		For readability and clarity.	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 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.	Modified “2 months” to “2 consecutive months”, where applicable.
		For clarity and to accommodate every other month (Q2M) dosing regimen.	Introduced the criteria for reduced predose LFT monitoring for patients on a every other month dosing schedule.
		To clarify the requirements for restarting dosing after the dosing pause. And re-organized the text for readability.	Section been updated.
		To clarify the rule of dosing restart.	Added a footnote for Fig 1 “Note: Restart following dosing pause to occur only once centrally measured AT activity levels ≥22%.”

Amendment number	Date approved	Rationale	Description of statistical changes
		For clarity.	Added a footnote: “See rules and exceptions as described above in Section 6.5.1.3. “.
		To allow for source data collection to support a better interpretation of biliary-related events.	Newly included additional evaluations to be performed for participants undergoing cholecystectomy.
		For better interpretation/narrative if participant undergo cholecystectomy.	Added cross reference to Section 9.1.7.2 regarding the instructions of additional evaluations if participants undergoing cholecystectomy.
		For clarity and consider the context of fitusiran on pause in the year 2020.	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.	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.	Specified that the interim analysis will be describe in the SAP.
		For clarity.	In Table 15 and 16, added a footnote regarding the ADA sampling timepoint on PR Months 24 and 36.
		For clarity.	Updated the definition of major dental surgery by including “or any tooth implantation”.
		Cosmetic, to follow the updated protocol template.	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.
		Administrative change.	Amendment history of previous version (ie, Amended protocol 08) was newly inserted in the current document Section 18.6 Protocol amendment history.
		To improve flexibility of patients and facilitate trial operation practice.	Added “approximately“ prior to “monthly intervals” of safety FU visits where applicable.
		For clarity.	Added “major” prior to “operative procedure” in perioperative

			assessment or management where applicable.
Amendment number	**Date approved**	**Rationale**	**Description of statistical changes**
		To correct the typo.	Used “EQ-5D-5L” instead of “EQ-5D”, “QoL” instead of “QOL”. Abbreviations been updated accordingly.
		Minor, therefore, have not been summarized.	Minor editorial, typo error corrections and document formatting revisions.

2.6 OTHER MODIFICATIONS MADE TO THE STATISTICAL ANALYSIS PLAN

This section summarizes other changes to the SAP during this amendment, based on interpretation of the Protocol.

Other SAP amendment changes

Description of change to SAP	Reason for revision
Kaplan-Meier (Time-to-event) analyses deleted from SAP Section 6.5.	The protocol specifies only that the times between successive bleeds be summarized descriptively.
Replace lab analysis using CTCAE by PCSA. Lab analysis by NCI CTCAE grade and shift tables are removed in Section 6.8.3 since PCSA analysis will be performed. Vital sign by PCSA is added in Section 6.8.4.	To be aligned with Sanofi’s standard analysis for Lab and vital sign.
Treatment period is defined to be the onset period plus the efficacy period.	The term “treatment period” is defined in Section 6.3 for consistency with other Fitusiran studies.
The ‘treatment policy strategy’ of analyzing the ABR is added to the primary analysis.	Added in Section 6.3.1 for consistency and comparison with other Fitusiran studies.
In the LTE14762) study we will consider untreated bleeds as well as treated bleeds in efficacy analyses.	Modifications made to Section 6.3 to the effect that additional analyses will be performed which will include all bleeds, both treated and untreated.
Concomitant medication was removed from safety variables in Section 3.2.4.	Typo corrected.
‘Patient’ was replaced by ‘participant’ throughout the document except for description of study design.	Align with company standard.
Analysis sets are defined for participants receiving original dose and regimen and participants receiving revised dose and regimen separately. Covid unaffected sets and full analysis sets are described in Section 4.	Treatment regimens are different before and after the dosing pause in 2020. Analysis sets are refined accordingly. Inclusion of covid unaffected sets to evaluate the impact of pandemic on the study. Inclusion of full analysis sets for efficacy analysis.

Description of change to SAP	Reason for revision
Description of intercurrent events is updated in Section 6.3..	Inclusion of 2020 voluntary dose pause. Update the definition of missing 2 consecutive dose for revised dose and regimen.
An additional baseline defined for safety analysis after the 2020 dosing pause.	Given the duration of voluntary dose pause in 2020, an additional baseline for selected safety endpoints is added to better evaluate the safety profile of revised dose and regimen.
Imputation rule for AE is updated in Section 5.8.	Align with Sanofi standard.
Inclusion of analysis window for revised dose and regimen.	Describe the analysis window for revised dose and regimen.
Specify analysis in general will be performed under original dose and regimen and under revised dose and regimen separately in Section 6. Describe planned analysis under revised dose and regimen.	To better evaluate the safety and long-term efficacy of revised dose and regimen.
Describe analysis for dosing interruption periods in Section 6.5.	To evaluate the AT recovery and bleeding during dosing pause in 2017 clinical hold and 2020 voluntary dose pause.
Describe algorithm of identifying cholecystitis and cholelithiasis in Section 6.8.2.	Align with other studies of fitusiran.
Describe analysis of liver function in Section 6.8.3	Additional analysis of liver function.
Description of subgroups to be analyzed in Section 6.11.	Inclusion of subgroups to be analyzed. Given the extended duration of treatment post TDR14767(ALN-AT3SC-001), the treatment type before parent study entry has limited impact on efficacy evaluation. Subgroup analysis of treatment type before enrollment into TDR14767(ALN-AT3SC-001) will be removed.

2.7 MODIFICATION MADE IN SAP TO THE STATISTICAL SECTION IN PROTOCOL

Description in SAP	Rationale	Description in Protocol
The analysis periods are defined in Section 6.3. The start of analysis periods is the date of fitusiran with at least 20mg since parent study entry.	Prior exposure on fitusiran in TDR14767(ALN-AT3SC-001) may impact the efficacy evaluation in LTE14762. The analysis will incorporate the parent study data and extension study data for a comprehensive assessment of efficacy on bleeding.	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.

3 OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVES

3.1.1 Primary objective

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

3.1.2 Secondary objectives

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.

3.1.3 Exploratory objectives

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

3.2 ENDPOINTS

3.2.1 Efficacy endpoints

Annualized bleeding rate (ABR) during the efficacy period

Annualized spontaneous bleeding rate during the efficacy period

Annualized joint bleeding rate during the efficacy period

Time intervals between bleeding events

Annualized weight-adjusted consumption of FVIII, FIX and BPA

Quality of life (QoL) measured by EuroQol 5-dimension 5-level (EQ-5D-5L) score

QoL measured by Haem-A-QoL score.

3.2.2 Pharmacokinetic endpoints

Plasma PK parameters of ALN-AT3SC

Urine PK parameters of ALN-AT3SC.

3.2.3 Pharmacodynamic endpoints

AT activity level over time

TG over time.

3.2.4 Safety variables

Adverse events (AE)

Clinical laboratory parameters

Vital signs

12-lead ECGs

Physical examinations.

3.2.5 Antidrug antibody endpoints

Incidence and titer of antidrug antibodies to fitusiran.

4 PARTICIPANT POPULATION

The following populations/analysis sets may be evaluated and used for presentation of the data.

Safety analysis set 1: All participants who receive at least a partial dose of study drug during the LTE14762 study under the original dose and regimen (ie, before the 2020 voluntary dose pause). The analysis set will be the main analysis set for analysis under original dose and regimen except for efficacy analysis and pharmacodynamics analysis.

Safety analysis set 2: All participants who receive at least a partial dose of study drug during the LTE14762 study under the revised dose and regimen (ie, after the 2020 voluntary dose pause). The analysis set will be used in safety analysis under revised dose and regimen. The analysis set will be the main analysis set for analysis under revised dose and regimen except for efficacy analysis and pharmacodynamics analysis.

Full analysis set 1: All participants in safety analysis set 1. The analysis set will be used in efficacy analysis and pharmacodynamics analysis under original dose and regimen.

Full analysis set 2: All participants in safety analysis set 2. The analysis set will be used in efficacy analysis and pharmacodynamics analysis under revised dose and regimen.

Per protocol set 1: All participants in the safety analysis set 1 who have no major protocol violations under the original dose and regimen in the following categories

- Failure to meet key eligibility criteria, which will be identified prior to database lock
- Prophylactic use of factor treatment or BPA (except for prophylaxis of bleeding in patients who require procedures or surgeries)

The protocol violation will be manually reviewed and adjudicated prior to database lock.

Per protocol set 2: All participants in the safety analysis set 2 who have no major protocol violations under the revised dose and regimen in the following categories

- Failure to meet key eligibility criteria, which will be identified prior to database lock
- Prophylactic use of factor treatment or BPA(except for prophylaxis of bleeding in patients who require procedures or surgeries)

The protocol violation will be manually reviewed and adjudicated prior to database lock.

PK analysis set 1: All participants who receive at least one dose of study drug and have at least 1 blood sample collection post-dose to determine plasma concentrations of study drug during the LTE14762 study under the original dose and regimen (ie, before the 2020 voluntary dose pause).

PK analysis set 2: All participants who receive at least one dose of study drug and have at least 1 blood sample collection post-dose to determine plasma concentrations of study drug during the LTE14762 study under the revised dose and regimen (ie, after the 2020 voluntary dose pause).

PD analysis set 1: All participants who receive at least one partial dose of study drug and have at least 1 blood sample collection post-dose to determine plasma AT and TG levels during the LTE14762 study under the original dose and regimen (ie, before the 2020 voluntary dose pause).

PD analysis set 2: All participants who receive at least one partial dose of study drug and have at least 1 blood sample collection post dose to determine plasma AT and TG levels during the LTE14762 study under the revised dose and regimen (ie, after the 2020 voluntary dose pause).

Operative procedure analysis set 1: All participants who received at least one partial dose of study drug and underwent at least 1 operative procedure during the LTE14762 study under the original dose and regimen (ie, before the 2020 voluntary dose pause).

Operative procedure analysis set 2: All participants who received at least one partial dose of study drug and underwent at least 1 operative procedure during the LTE14762 study under the revised dose and regimen (ie, after the 2020 voluntary dose pause).

Covid-19 unaffected set 1: All participants who have no major or critical protocol deviations due to Covid-19 during the study period under the original dose and regimen (ie, before the 2020 voluntary dose pause).

Covid-19 unaffected set 2: All participants who have no major or critical protocol deviations due to Covid-19 during the study period under the revised dose and regimen (ie, after the 2020 voluntary dose pause).

The Safety Analysis Set 1 and Safety Analysis Set 2 will be the primary sets for safety assessments, and for analyses of the efficacy and durability of fitusiran treatment. The PK Analysis Set 1 and PK Analysis Set 2 will be used for PK analysis and the PD Analysis Set 1 and PD Analysis Set 2 will be used for PD analyses. The PP Analysis set 1 and PP Analysis set 2 will also be used to assess the long-term efficacy of fitusiran treatment. The Operative procedure analysis set 1 and Operative procedure analysis set 2 will be used to assess safety and hemostatic efficacy in participants undergoing operative procedures while on study.

5 GENERAL STATISTICAL METHODS

5.1 SAMPLE SIZE JUSTIFICATION

Sample size was based on the number of participants who enrolled in the parent study and subsequently received doses of fitusiran while enrolled in the LTE14762 study, and not on statistical considerations.

5.2 GENERAL METHODS

Both efficacy and safety analysis under the original and revised dose regimens will be analyzed separately, unless otherwise specified. The data collected during the 2020 voluntary dose pause will be analyzed along with the pre-pause data.

A significant dose is defined as any single dose of fitusiran that is greater than or equal to 20 mg. Before the voluntary dose pause, the analysis period for efficacy endpoints starts from the date of first significant dose up to the earlier of 2020 voluntary dose pause date or the last day of study follow-up. For safety endpoints, the analysis will be performed based on LTE14762 study period data only up until the dose restart date. Date of first significant dose in the TDR14767(ALN-AT3SC-001) and LTE14762 study/studies will be designated as Treatment Day 1; there will be no Treatment Day 0. Participants who receive doses (either weight-dependent or weight-independent) of at least 20 mg but less than 75 mg will be "classified" as "50 mg" participants, while participants receiving doses of greater than or equal to 75 mg will be "classified" as "80 mg" participants (except PK analysis in which actual dose on Day of PK sample collection will be used). However, for purposes of efficacy and safety analyses and summaries in the final CSR report for the LTE14762 study, the classification of each participant under the original dose and regimen will be according to the fixed dose to which they are eventually taken by the end of the LTE14762 study original dose period. For example, participants who received a 50 mg dose in TDR14767(ALN-AT3SC-001) or LTE14762 and then were switched to 80 mg dose at some point in time during the LTE14762 study, are classified in the LTE14762 study as "80 mg" participants (except for PK analyses). Treatment after the volunteer dose pause will be treated as each participant's treatment sequence.

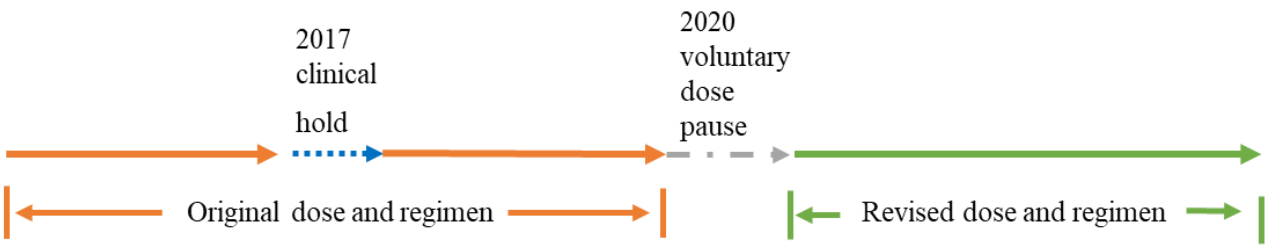
Treatment Days under the original dose and regimen will be calculated as evaluation date – first significant dose date +1 and pre-treatment days will be calculated as evaluation date – first significant dose date. (The pre-treatment day formula applies when evaluation date < first significant dose date; ie, for example, there will be pre-treatment Days … -3, -2, -1, then treatment Day 1, 2, 3, 4, …; there is no "pre-Treatment Day 0" nor is there any "Treatment Day 0").

We also define Study Days in the LTE14762 study as the number of days from first significant dose in LTE14762 and calculate similarly as the Treatment Days. For participants who received first significant dose in LTE14762, the Study Days is the same as the Treatment Days.

For participants under the revised dose and regimen, both efficacy and safety data will be analyzed from the dose re-start Day 1 up until the last day of study follow-up.

Treatment day after the dose re-start will be calculated as evaluation date – first dose date after dose re-start + 1 (days). It should be not applicable for assessments before the dose re-start. A summary of study periods and start day in analysis is outlined in Figure 1

Figure 1 Study periods and analysis start day summary



	Original dose and regimen	2017 clinical hold/2020 voluntary dose pause	Revised dose and regimen
Efficacy analysis	Starts from first significant dose of fitusiran in TDR14767(ALN-AT3SC-001) or LTE14762 and in terms of treatment days.	Starts from the 29th days after last dose date before the hold/pause	Starts from first dose date of revised dose and regimen and in terms of treatment days
Safety analysis	Starts from first significant dose of fitusiran in LTE14762 and in terms of study days	Starts from the day after last dose date before the hold/pause and in terms of study days	Starts from first dose date of revised dose and regimen and in terms of study days

Summary statistics will be reported by analysis visits defined in Section 5.10 below. Unless otherwise noted, tables under both the original and revised dose regimens will be presented by hemophilia type, inhibitor type and overall. Participants who received a significant dose in TDR14767(ALN-AT3SC-001) will be considered as a subgroup in the analysis under the original dose and regimen. Details will be specified in the Section 6.11.

Categorical data summary will include the number and percentage of participants within each category, with a category for missing data. Continuous data summary will include descriptive statistics - the number of participants, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum, and maximum. The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures and derived listings. Minimum and maximum values will be reported with the same

precision as the units of measure. The other statistics will be reported with 1 greater decimal place. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

To be consistent with the compound level wording, 'revised dose and regimen' will be shown as 'recommended dose and regimen' in the statistical output.

5.3 COMPUTING ENVIRONMENT

All statistical analyses will be performed using SAS statistical software Version 9.4 (or later), unless otherwise noted.

5.4 TIMING OF ANALYSES

Data will be analyzed as needed; the final analyses will be conducted after the last participant completes the last study assessment or withdraws from the study.

5.5 BASELINE DEFINITIONS

Baseline demographics and disease characteristics will be the baseline from both the parent study TDR14767(ALN-AT3SC-001) and study LTE14762. The following disease characteristics will be taken from the parent study:

- hemophilia type
- time since diagnosis
- biological phenotype
- prior treatment type
- historical ABR
- hepatitis C status
- historical ABR
- historical hemophilia clinic visit 6 months prior to parent study entry

Baseline assessment for by-visit analyses is defined as the last non-missing value on or before first significant Treatment Day and/or LTE14762 Study Day (ie, baseline on or before the first significant treatment day will be considered for all efficacy endpoints while baseline on or before the first LTE14762 study day will be considered for all safety endpoints). These baselines will be considered in analyses under both original and revised dose and regimen as main analysis.

An additional baseline under the revised dose and regimen is defined as the non-missing assessment on or prior to the revised dose re-start date regardless of dose regimen. It is applicable only for participant who consented to the protocol amendment 8. This baseline will be analyzed in selected safety endpoints under the revised dose and regimen. Detailed information will be specified in Section 6.8.

5.6 RANDOMIZATION STRATIFICATION FACTORS

Not applicable.

5.7 MULTIPLE COMPARISONS/MULTIPLICITY

Not applicable.

5.8 MISSING DATA

Data will be analyzed as observed. No imputation for missing data will be performed, except in the case of missing questionnaire data and adverse event data. Missing questionnaire data will be handled according to universally accepted standards. If the assessment of the relationship to fitusiran is missing for an AE, this AE will be assumed as related to fitusiran. If the severity is missing for one of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

5.9 PROTOCOL DEVIATIONS

Major protocol deviations will be identified before final analysis.

5.10 DERIVED ANALYSIS VISIT WINDOWS

For LTE14762 by-visit analyses under the original dose and regimen such as lab and vital sign parameters, it is expected that all 002 study visits will occur according to the protocol schedule of assessments. Analysis visits will be assigned based on LTE14762 evaluation visits as recorded on the CRF even if the assessment is outside of the window for that study visit.

For TDR14767(ALN-AT3SC-001)/ LTE14762 combined by-visit analyses under the original dose and regimen such as PD and QoL endpoints, analysis visits will be defined as follows.

For participants whose first “significant” dose of fitusiran was administered in TDR14767(ALN-AT3SC-001) (eg, this could only occur in the MD cohort [Part C and Part D]; other cohorts are administered relatively small doses of fitusiran),

a) Analysis visits for all TDR14767(ALN-AT3SC-001) assessments will be first assigned based on TDR14767(ALN-AT3SC-001) evaluation visit as recorded on the CRF and will be adjusted, if necessary, so that the window of the TDR14767(ALN-AT3SC-001) assessment overlaps as much as possible with the LTE14762 scheduling.

b) Analysis visits will be derived for the LTE14762 Day 1 assessment based on the Treatment Days and will be assigned for subsequent visits based on LTE14762 evaluation visit as recorded on the CRF. For example, Haem-A-Qol is assessed quarterly in the 1st two years and then yearly after in LTE14762. If the Treatment Days for Day 1 visit is within 18 months +/-1.5 month, then analysis visit for Day 1 visit

will be derived as Month 18, and the subsequent analysis visits will be assigned quarterly or yearly after Month 18 accordingly.

For participants whose first "significant" dose of fitusiran was administered in LTE14762, Analysis visits under the original dose and regimen will be assigned based on LTE14762 evaluation visit as recorded on the CRF.

For LTE14762 by-visit analyses under the revised dose and regimen, analysis visits for scheduled visits will be defined based on CRF reported VISIT, even if the assessment is outside of the window for that study visit.

- For participant who had dose reduction after the dose pause, the analysis visit will be assigned based on the CRF reported PR VISIT (PRxx) as following example for the first 18 months after dose pause for the revised dose regimen scenarios. For unscheduled visit, the analysis visit will be populated based on treatment day after dose re-start (ie, Date of PR Day 1). The analysis visit window will be derived as the middle-point of the target day between the 2 consecutive scheduled visits for each of the assessment. The target day is calculated as 28 days of visit interval times corresponding scheduled months plus 1. The treatment day after the volunteer dose pause is defined in Section 5.2

Table 2 – Analysis visit schedule after the 2020 dose pause

CRF reported VISIT		Analysis visit	Target day	Binning algorithm	
No dose escalation after pause	Dose escalated to 50QM			Lower bound	Upper bound
50Q2M Day1	50Q2M Day1	PR Day 1	1	1	1
50Q2M PRM1	50Q2M PRM1	PR Month 1	29	2	42
50Q2M PRM2	50Q2M PRM2	PR Month 2	57	43	70
50Q2M PRM3	50Q2M PRM3	PR Month 3	85	71	98
50Q2M PRM4	50Q2M PRM4	PR Month 4	113	99	126
50Q2M PRM5	50Q2M PRM5	PR Month 5	141	127	154
50Q2M PRM6	50Q2M PRM6	PR Month 6	169	155	182
50Q2M PRM7	50QM PRM1	PR Month 7	197	183	210
50Q2M PRM8	50QM PRM2	PR Month 8	225	211	238
50Q2M PRM9	50QM PRM3	PR Month 9	253	239	266
50Q2M PRM10	50QM PRM4	PR Month 10	281	267	294
50Q2M PRM11	50QM PRM5	PR Month 11	309	295	322
50Q2M PRM12	50QM PRM6	PR Month 12	337	323	350
50Q2M PRM13	50QM PRM7	PR Month 13	365	351	378
50Q2M PRM14	50QM PRM8	PR Month 14	393	379	406
50Q2M PRM15	50QM PRM9	PR Month 15	421	407	434
50Q2M PRM16	50QM PRM10	PR Month 16	449	435	462
50Q2M PRM17	50QM PRM11	PR Month 17	477	463	490
50Q2M PRM18	50QM PRM12	PR Month 18	505	491	518

- For participant who remain the original dose regimen after the dose pause, the analysis visit will be derived based on original visit schedule (ie, Month xx), which will be reported following the original visit scheme. The first dose date after the dose pause will be assigned as Day1. The subsequent visits can be assigned based on the first visit accordingly. For example, the first visit after dose re-start is reported as “Month 36”, then the next visit is reported as “Month 37”. The Month 36 visit should be assigned as “PR Day 1” and the Month 37 should be assigned as “PR Month 1”. For unscheduled visit, the analysis visit will be populated based on treatment day after dose re-start. The analysis visit window will be derived as the middle-point of the target day between the 2 consecutive scheduled visits for each of the assessment. The target day is calculated as 30 days of visit interval times corresponding scheduled months plus 1. The treatment day after the volunteer dose pause is defined in Section 5.2.

6 STATISTICAL ANALYSES

6.1 PARTICIPANT DISPOSITION

Participant disposition (all participants) will be summarized before and after the 2020 voluntary dose pause separately including participants enrolled, participants in each analysis population/set, participants who completed the study, participants who discontinue study drug with primary reasons for study drug discontinuation, participants who withdraw prior to completing the study with primary reason for withdrawal, and period of clinical hold or voluntary dose pause for each participant.

6.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline disease characteristics will be summarized for the safety analysis set 1 and safety analysis set 2. Demographics will include age, age group, gender, race, ethnicity, height, weight, body mass index (BMI), and region. Baseline hemophilia disease characteristics will be reported from parent study TDR14767(ALN-AT3SC-001) and will include hemophilia type, biological phenotype, historical ABR based on 6-month bleed history prior to parent study entry and historical number of hemophilia clinic visits.

6.3 EFFICACY

Bleeding event definitions

A bleeding episode is defined as any occurrence of hemorrhage that may require administration of BPA infusion or factor concentrates. Bleeding episodes sustained during sports and recreation will be counted as traumatic bleeding episodes.

Bleeding or any symptoms of bleeding at the same location that occur within 72 hours of the last injection used to treat a bleed or 72 hours after an untreated bleed at that location will be considered a part of the original bleeding event and will count as one bleeding episode. Any bleeding symptoms that begin more than 72 hours from the last injection used to treat a bleed or 72 hours after an untreated bleed at that location will constitute a new bleeding event.

The following definitions of bleeding event types, based on consensus opinion of International Society on Thrombosis and Haemostasis (ISTH), will apply:

Traumatic bleed: caused by a known injury or trauma, including sports and recreation

Spontaneous bleed: that occurs for no apparent or known reason

Joint bleed: an unusual sensation in the joint (“aura”) in combination with either of

- increasing swelling/warmth on the skin over the joint
- increasing pain
- progressive loss of range of motion

- progressive difficulty in using the limb.

Muscle bleed: 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 events occur within a consecutive 6-month period has occurred; if ≤2 bleeding events occur in a joint within a consecutive 12-month period the joint will be excluded from target joint.

Traumatic bleeds that occur in different locations simultaneously (same date/time) in the same participant will be considered as one bleeding episode. Spontaneous bleeds that occur simultaneously (same date/time) in different locations in the same participant will be considered as separate bleeds.

Efficacy analysis will focus on observed data as collected, unless otherwise specified. Only bleeding episodes that are treated with BPA/factor will be include in the primary analysis of endpoints evaluating bleeding; however additional analyses will be performed which will include all bleeds, both treated and untreated.

Definition of analysis period

The analysis periods will be defined separately before and after the volunteer dose pause.

The original dose and regimen:

- Onset period: The onset period is defined as the period of time consisting of the first 28 days: Treatment Day 1 to Treatment Day 28 (of TDR14767(ALN-AT3SC-001) and LTE14762) (see above - definition of "Treatment Day"); this is the period of time during which the AT lowering capacity of fitusiran is increasing but has not yet reached therapeutic levels.
- Efficacy period 1: The efficacy period 1 is defined as Treatment Day 29 to earlier of End of study date before the dose pause or the last fitusiran administration date before the dose pause + 28 days, whichever comes first.
- Treatment period 1: The treatment period 1 is defined to be the onset period plus the efficacy period 1.

The revised dose and regimen:

- Dose adjustment period: The dose adjustment period is defined as the dose re-start Day 1 to the earlier of dose re-start Day 168 or the end of study.
- Efficacy period 2: The efficacy period 2 is defined as the dose re-start Day 169 to the end of study visit
- Treatment period 2: The treatment period 2 is defined to be the dose adjustment period plus the efficacy period 2.

All the analysis periods will exclude the period of following intercurrent events to avoid confounding of treatment effect for the primary efficacy analysis based on On-Treatment Strategy:

Intercurrent events:

I. "Dose interruption periods":

   a. Gap between TDR14767(ALN-AT3SC-001)/ LTE14762 study >28 days and skips at least two doses in the gap: Exclude events occurring on dates starting from the date of the last dose in 001 +29 days to the date of first dose in LTE14762 +28 days and gap duration >84 days.

   b. Clinical hold/dose pause period during LTE14762 study: Exclude events occurring on dates starting from the date of the last dose before dose interruption +29 days to the date of dose resumption +28 days and on-hold duration > 84 days.

      - Dose hold in 2017: The last dose before dose interruption is defined as the last fitusiran administration before 2017[redacted]. The first dose after dose resumption is defined as the first fitusiran administration after 2017[redacted].

      - Voluntary dose pause in 2020: The last dose before dose interruption is defined as the last fitusiran administration before 2020[redacted]. The first dose after dose resumption is defined as the first fitusiran administration after 2021[redacted].

   c. Missing two consecutive doses in LTE14762 (eg, a participant skips at least two consecutive scheduled doses): If participant under Q2M regimen before the dose interruption, then exclude events occurring on dates starting from the date of the last dose before the dose interruption + 57 days to the date of the dose resumption + 56 days. If participant under QM regimen before the dose interruption, then excluded events from the date of the last dose before the dose interruption + 29 days to the date of the dose resumption + 28 days. The missing two consecutive doses will be considered separately before and after the dose pause in 2020.

   d. Fitusiran treatment discontinuation in LTE14762: Exclude events occurring on any dates starting from the date of the last dose +29 days if the last dose regimen is QM (ie, until the end of the study.) If the last dose regimen is Q2M, then the start date of this intercurrent event should be last dose + 57 days.

II. Perioperative period of major surgery and major trauma is defined as the day of the surgery or trauma through the final day on which supplemental hemostatic or antithrombotic treatments are administered as part of the perioperative treatment plan.

III. Perioperative period of minor surgery is defined as the perioperative period of surgery as defined for major surgery (see above) or to 72 hours from the end of surgery, whichever is later.

IV. Period of antithrombin treatment defined as the first day of antithrombin treatment through the final day on which antithrombin or other anticoagulant therapies are administered +5 half-lives.

V. After treatment with emicizumab.

6.3.1 Analysis of long-term durability and efficacy

6.3.1.1 Annualized bleeding rate

The ABR efficacy analysis will include all bleeding events occurring in the efficacy period. The ABR will be annualized for each participant using the following formula:

$$\text{Annualized bleeding rate (ABR)} = \frac{\text{total number of bleeding events}}{\text{total number of days in the respective period}} \times 365.25$$

The primary efficacy analysis will consist of the ABR results based on the "on-treatment strategy" during the efficacy period (efficacy period as strictly defined in Section 6.3 above, excluding the periods of intercurrent events). The "on-treatment strategy" analysis will also be performed for the onset period and the treatment period. The "treatment policy strategy" analysis, will be performed for the treatment period only, and will consist of the ABR calculations applied to ***all*** (treated) bleeds (even including surgery periods), taking place during the analysis period of interest only excluding the gap between TDR14767(ALN-AT3SC-001) and LTE14762 where the bleeds were not collected. ABR will be estimated (with 95% CI) using a negative binomial model adjusted by TDR14767(ALN-AT3SC-001) study baseline ABR. No imputations of missing data will be performed in the ABR analyses. The ABR analysis under the original dose and regimen will be performed for the entire efficacy period 1 and also for the treatment period 1 and onset period (for the "on-treatment strategy"), as well as by year for the treatment period 1 (both on-treatment and treatment policy strategies) in order to demonstrate the durability of the prophylactic maintenance. Model based ABR will be provided when there are at least 3 participants in the group and model converges for by-year analysis. Also, additional analyses will be performed including all bleeds, both "treated" and "untreated".

ABR under the revised dose and regimen after the dose pause for treated bleeding events and all bleeding events during the dose adjustment period, efficacy period 2 and treatment period 2 based on on-treatment strategy will be analyzed respectively. ABR for treated bleeding events during the treatment period 2 will also be summarized based on on-treatment strategy every 6 months. Similar ABR analysis during treatment period 2 based on treatment policy (ignoring all intercurrent events) will be performed as well.

The ABR primary analyses described above will be performed again on the PP population to support long-term efficacy of fitusiran and robustness of result. If per-protocol population is the same set of participants as the safety population, then analysis based on safety population will be provided only.

6.3.1.2 Bleed-free duration

Bleed-free duration (BFD) for each participant will be calculated as the time interval between 2 protocol-defined treated bleeding events, excluding bleeding events that occur during the intercurrent periods during both of the efficacy periods based on on-treatment strategy respectively. If participant don't have any bleeding event in each of the efficacy period, the overall duration of the corresponding efficacy period will be the bleed-free duration. ABR and maximum BFD (after 1st significant dose) will be summarized descriptively. A similar calculation

of bleed-free duration considering all bleeding events will be performed for clinical hold or voluntary dose pause analysis described in Section 6.5.

6.3.2 Quality of life

Descriptive summary for QoL questionnaires will be provided before and after the 2020 voluntary dose pause respectively.

6.3.2.1 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of QoL outcome. Index values and visual analogue scale (VAS) scores and their changes from Treatment baseline to each post-baseline visit will be summarized descriptively. Numbers and percentages of participant by level and dichotomized level (1 = “no problems”, 2 to 5 = “some problems”) of each dimension will be reported.

6.3.2.2 Haem-A-QoI

The Haem-A-QoL includes 46 items contributing to 10 QoL domains (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality). Scoring for each item is based on a 5-point Likert scale (never, rarely, sometimes, often, and all the time), and higher scores represent greater impairment. Total score, domain scores, standardized scale scores, and transformed scale scores and their changes from treatment baseline to each post-baseline visit will be summarized descriptively.

6.3.3 Annualized weight-adjusted consumption of BPA and factor

Weight-adjusted factor/BPA usage will be calculated programmatically. Number of factor or BPA injections per bleed, weight adjusted total dose per injection and total dose per bleed will be summarized descriptively. Additional summary will be provided by bleed location, causality and severity.

6.4 PHARMACODYNAMIC ANALYSIS

Pharmacodynamic analyses before the dose pause will be conducted using the PD analysis set 1. AT activity, AT lowering (% reduction from Treatment baseline) and peak thrombin values will be summarized at each post-baseline visit descriptively. The baseline under the original dose and regimen will be the last non-missing assessment before the first significant dose. Only evaluable PD result will be included in the analysis. The criteria listed in the Table 3.

Table 3 - PD assessment evaluable criteria

	Criteria description	AT	TG
Criteria 1	Assessments collected during any of the dose interruption period[a] will be excluded.	X	X
Criteria 2	Assessments collected during the antithrombin treatment[b] period or within 5 half-lives after the antithrombin treatment administration will be excluded.	X	X
Criteria 3	Assessments collected within 48 hours of factor, BPA or antifibrinolytic administration will be excluded.		X
Criteria 4	Assessment collected at one visit without AUC assessment available on the same visit will be excluded.		X

a Refers to section 6.3 intercurrent event definition.

b The antithrombin treatment includes Heparin, Antithrombin Concentrate and Factor Xa inhibitors. All the other antithrombin treatment will be adjudicated by Sanofi medical team.

Similar pharmacodynamic analyses after the 2020 voluntary dose pause will be performed based on the PD analysis set 2 by treatment sequence specified in Section 5.2.

6.4.1 AT lowering and peak thrombin

Correlation between AT (actual AT activity and AT lowering) and peak TG will be computed on paired assessments, where both parameters are measured on the same day. Log transformation may be used.

6.5 ANALYSES DURING DOSE INTERRUPTION

For participants who had clinical hold in 2017, the following exploratory analyses will be performed:

Rate of AT recovery since last dose before interruption will be summarized descriptively. AT activity over time since last dose before interruption will plotted.

AT activity and peak TG over time since last dose before interruption will be plotted.

ABR before, during and after the interruption period will be summarized descriptively. Similarly, maximum bleed free duration for treated bleeding events before and after interruption period will be summarized descriptively. ABR and maximum bleed free duration before and after the interruption period will be analyzed based on efficacy period and on-treatment strategy considering all intercurrent events. Bleeding events during the first 29 days after dose resumption will not be considered based on on-treatment strategy for participants whose 2017 dose hold period >84 days as outlined in Section 6.3. ABR during the interruption period will consider intercurrent events II – V based on on-treatment strategy. The interruption period will start from 29 days after last dose before interruption till the day before first dose at resumption of treatment.

ABR before, during and after the interruption period will be summarized descriptively. Similarly, maximum bleed free duration for all bleeding events before and after interruption period will be summarized descriptively. ABR and maximum bleed free duration before and after the interruption period will be analyzed based on efficacy period and on-treatment strategy considering all intercurrent events. Bleeding events during the first 29 days after dose resumption

will not be considered based on on-treatment strategy for participants whose 2017 dose hold period >84 days as outlined in Section 6.3. ABR during the interruption period will consider intercurrent events II – V based on on-treatment strategy. The interruption period will start from 29 days after last dose before interruption till the day before first dose at resumption of treatment.

For participant who had voluntary dose pause interruption in 2020, similar analysis will be done for the AT/TG assessments, ABR and maximum bleed free duration.

6.6 ADDITIONAL EXPLORATORY ANALYSES

For participants who undergo operative procedures during the study, the total number of participants 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. Other data on surgical cases, including factor/BPA use, may be described in narrative form.

6.7 PHARMACOKINETIC ANALYSIS

Pharmacokinetic analyses will be conducted using the PK analysis set 1 and PK analysis set 2. Plasma PK parameters will be estimated using a population PK approach. The population PK analysis will be described in a separate population PK analysis plan. In addition to performing population PK 32onhealt, PK parameters will also be estimated using non-compartmental analysis in participants who opted to participate in extensive PK sampling during one or more of the PK sampling periods (Day 1, Month 12, Month 24).

PK parameters to be estimated using non-compartmental analysis will include, but will not be limited to: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), apparent clearance (CL/F), and apparent volume of distribution (V/F). The amount of fitusiran excreted in 0-24 h urine from a subset of participants who opted to participate in urine collections, will also be estimated using non-compartmental analysis. Other plasma and/or urine PK parameters may also be calculated, if considered appropriate.

6.8 SAFETY ANALYSES

Safety analyses will be conducted using the safety analysis set 1 and safety analysis set 2. Only the safety data occurred in LTE14762 will be summarized unless specified otherwise.

Safety analysis under the original dose and regimen (i.e. before the 2020 voluntary dose pause) and the revised dose and regimen (i.e. after the 2020 voluntary dose pause) will be analyzed separately. The additional baseline prior to the revised dose regimen administration will be implemented for data collected under the revised dose and regimen. Similar descriptive summaries in reference to the additional baseline will be provided for laboratory, vital sign and ECG endpoints.

6.8.1 Study drug exposure

Duration of exposure (years) and the number of study drug doses used from Treatment Day 1 in the TDR14767(ALN-AT3SC-001)/LTE14762 under the original dose and regimen will be summarized descriptively, where duration of exposure (days) = date of the last dose of study drug – the date of the first significant dose of study drug + 28 days excluding the gaps between TDR14767(ALN-AT3SC-001)/LTE14762 and dose suspension in LTE14762. Duration of exposure and the number of study drug doses in LTE14762 study will be summarized similarly.

Duration of exposure under the revised dose and regimen will be summarized. If participant had the last dose under the Q2M dose frequency, the duration (days) = date of the last dose of fitusiran – the date of the first dose of fitusiran under the revised dose and regimen + 56 days. If participant had the last dose under the QM dose frequency, the duration (days) = date of the last dose of fitusiran – the date of the first dose of fitusiran under the revised dose and regimen + 28 days.

The overall duration of exposure regardless of revised dose from the first significant dose and/or from the first dose in the LTE14762 study until the end of study may also be summarized as needed. The planned dose intermittent period (Table 4) will be excluded from the overall duration of exposure.

Table 4 – Definition of planned dose intermittent periods

	Start date	End date	Note
Gap between parent and extension study	Last fitusiran dose date in parent study + 29 days	First fitusiran dose date in extension study – 1	If duration < 14 days, then no gap between the 2 studies.
2017 dose suspension	Last fitusiran dose before 01SEP2017 + 29 days	First fitusiran dose after 01SEP2017 – 1	If duration < 14 days, then no dose suspension period should be excluded.
2020 dose suspension	Last fitusiran dose date before 31Oct2020 + 29 days	First fitusiran dose after 26Jan2021 – 1	If duration < 14 days, then no dose suspension period should be excluded

Note: Duration is calculated as end date – start date +1 for each dose intermittent periods.

6.8.2 Adverse events

Adverse events (AE) analysis will include treatment-emergent events, with onset occurring in the LTE14762 study. (Note: All AEs collected in LTE14762 are considered TEAE because all participants received dose in TDR14767(ALN-AT3SC-001).)

All AEs will be coded using the MedDRA(version 25.1 or later) coding system and displayed in tables and data listings using system organ class (SOC) and preferred term (PT). AEs will be summarized by the numbers and percentages of participants reporting at least 1 AE, having at least 1 AE by primary SOC and PT. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. Participants who report multiple occurrences of the same AE (preferred term) will be classified according to the most related or most severe occurrence, respectively.

All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, unless specified otherwise. The SOC will be presented according to

international standards (MedDRA Internationally Agreed Order), and the preferred term will be sorted within each SOC in decreasing order of frequency.

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

1. ALT or AST elevations >3 × ULN
2. Suspected or confirmed thromboembolic events
3. Severe or serious injection site reactions (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 study drug.
4. Systemic (injection associated reactions (IARs), defined as hypersensitivity reactions which are related or possibly related to IMP.
5. Cholecystitis
6. Cholelithiasis

The identification of cholecystitis and cholelithiasis will be a combination of systematic search of higher level group term (HLGT) and AESI collected as it is in CRF. AEs whose HLGT fall into the categories listed below will be considered as AESI of cholecystitis and cholelithiasis:

1. Bile duct disorders,
2. Gallbladder disorders
3. Hepatic and hepatobiliary disorders

An overall summary of TEAEs will include the number and percentage of participants with any TEAE, any TEAE assessed by the Investigator as related to study drug (possibly related or definitely related), any serious TEAE (TESAE), any TESAE related to study drug, any TEAE of special interest; any AE/SAE leading to permanent study drug discontinuation, any TEAE/TESAE leading to study withdrawal, and any deaths. The TEAE onset within any major surgery period will be provided in a separate column in the overview summary statistics as well as in the overall column. They will be excluded from the rest of by-indication columns in the table.

Tabulations of TEAEs by SOC and PT excluding those AE onsets within major surgery period will be produced for the following:

1. TEAEs
2. TEAEs by severity
3. Treatment emergent SAEs
4. TEAEs related to study drug
5. Treatment emergent SAEs related to study drug
6. TEAEs leading to permanent study drug discontinuation
7. Treatment emergent SAEs leading to permanent study drug discontinuation
8. TEAEs leading to study withdrawal
9. Treatment emergent SAEs leading to study withdrawal
10. Treatment emergent AESI (Adverse Events of Special Interest)
11. TEAEs potentially consistent with Covid-19. These AEs will be identified based on SMQ group searching.

All AEs will be listed along with the information collected on those AEs, eg, AE relationship to study drug, AE outcome etc. By-participant listings will also be provided for the following: all participant deaths, all SAEs, and all AEs leading to permanent study drug discontinuation or study withdrawal, all AEs leading to death. AE onset during the major surgery period will also be included in each of the by-participant listing with major surgery flag.

The incidence rate of severe or serious ISRs will also be summarized. The incidence rate is defined as the number of severe or serious ISRs per study drug injection. If multiple ISRs occur between two consecutive injections, they will be counted under the first injection as 1 ISR.

Because of hepatitis C infected participant got enrolled in the TDR14767(ALN-AT3SC-001) study, participants with treatment emergent ALT or AST elevations > 3 ULN AESI will be analyzed based on their HCV status at the enrollment of LTE14762 study.

Additional summary of incidence rate for TEAE, SAE, AEs leading to permanent study drug discontinuation and AESI before and after the 2020 dose pause by primary SOC and PT will be provided.

6.8.3 Laboratory data

Clinical laboratory values will be expressed in standard international (SI) units. Laboratory data collected and recorded as below the limit of detection will be set equal to the lower limit of detection for the calculation of summary statistics.

For each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation studies and thyroid and liver function tests) from the central laboratory descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit. The descriptive statistics under the original dose and regimen will be provided from the LTE14762 study baseline up to the last assessment before the 2017 clinical hold. The baseline used for this analysis is LTE14762 study baseline. Similar by-visit summary will be provided under the revised dose and regimen from the dose resumption after 2020 voluntary dose pause up to the end of study. There are 2 baselines considered for this analysis, which are LTE14762 study baseline and dose resumption baseline on or before the dose resumption after the 2020 voluntary dose pause.

In order to address impact of 2017 and 2020 dose interruption, additional spaghetti plots using actual values will be provided for below laboratory parameters:

4. Alanine Aminotransferase (ALT),
5. Aspartate Aminotransferase (AST),
6. Total Bilirubin,
7. Alkaline Phosphatase,
8. D-Dimer,
9. Prothrombin Fragments 1 + 2 and
10. Fibrinogen.

All the assessments from central laboratory, including assessments performed during the 2017 and 2020 dose interruption periods, will be used for the plot. For those assessments collected during the 2017 and 2020 dose interruption periods, a different color will be used to distinguish these periods.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges (when available).

Listings will be produced for all participants with abnormal liver function tests defined as an ALT >3 × ULN or 3 × Baseline (for those participants with abnormal values at baseline), or AST >3 × ULN or 3 × Baseline (for those participants with abnormal values at baseline, at any time point. ("Baseline" here means LTE14762 baseline.) These listings will include each of the assessments specified in Tables 8 and 9 of the Protocol (Amendment 9).

Number of participants with at least one occurrence of AST/ALT >3 × ULN and at least 2 occurrence of AST/ALT >3 × ULN will be summarized descriptively. Time to first onset of AST/ALT >3 × ULN will be analyzed using Kaplan-Meier method. Participants who complete the study and do not have the event will censor at study completion date. Participants who do not complete the study under original dose and regimen will be censor at the earlier of last dose date under the original dose and regimen +28 days or the day before dose resumption. Participants who do not have the event under revised dose and regimen will be censored at last visit date as of data cutoff. If participants experienced the event of after AST/ALT >3 × ULN 2017 clinical hold under original dose and regimen, the 2017 clinical hold period will be excluded.

A table will be produced to summarize the number and percentage of participants in each of below categories at any time point during the duration of LTE14762) study.

1. ALT >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20 × ULN
2. AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20 × ULN
3. ALT or AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20 × ULN
4. ALP >1.5 × ULN
5. Total Bilirubin >1.5 & ≤2, >2 & ≤3, >3 & ≤5 and >5×ULN
6. Total Bilirubin > 2×ULN concurrent with ALT or AST > 3×ULN
7. INR >1.2×ULN

eDISH(evaludation of drug-induced serious hepatotoxicity) plots will be provided by indications. Number of participants in the following categories will be listed: cholestasis, potential Hy's law case, Temple's corollary range and normal range.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities (PCSA) will be provided. Both data from central laboratory and local laboratory will be considered in PCSA analysis. Additional liver function PCSA analysis by HCV status will be analyzed as well.

All the laboratory data analysis will not include assessment taken during the major surgery period. All laboratory data will be provided in data listings with identifier of assessment during the major surgery period. Out-of-range laboratory results and PCSA will be identified in the listings.

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 the protocol 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.

6.8.4 Vital signs and physical examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate. For data under the original dose and regimen, the descriptive summary will be provided from the LTE14762 study baseline up to the 2017 clinical dose pause. For data under the revised dose, the summary will be provided from the dose resumption up to the end of study. A summary table of PCSA will be provided. Abnormal PE results will be listed. All the vital sign and physical examination summary tables will not include assessment taken during the major surgery period. These results will be presented in listings with identifier of major surgery.

6.8.5 Electrocardiogram

Listings for 12-lead ECG will be provided. Additionally, PR, QRS, QT, Bazzett's (QTcB) and Fridericia's (QTcF) corrected QT and RR intervals will be summarized descriptively, where (QTcF) is calculated using the formula

$$\text{QTcF (ms)} = \text{QT (ms)} \cdot \sqrt[3]{\frac{HR\ (bpm)}{60}}$$

and where (QTcB) is calculated using the formula

$$\text{QTcB (ms)} = \text{QT (ms)} \cdot \sqrt{\frac{HR\ (bpm)}{60}}$$

For data under the original dose and regimen, the descriptive summary will be provided from the LTE14762 study baseline up to the 2017 clinical dose pause. For data under the revised dose, the summary will be provided from the dose resumption up to the end of study.

6.8.6 Medical history

Medical history will be summarized by MedDRA(version 25.1 or later) coding system SOC and PT. A participant contributes only once to the count for a given condition (overall, by SOC, by PT).

6.8.7 Concomitant medications

Concomitant medication is defined as all medications other than study drug administered to a participant during the study. (All AE and CM collected in the study should be included in the analyses because all participants received dose in TDR14767(ALN-AT3SC-001).) Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic

therapeutic class (ATC) and preferred term. Concomitant medications excluding the medication used during the major surgery period will be summarized. A separate summary of concomitant medication administrated during the major surgery period will also be provided.

6.8.8 Bleed management guidelines

Compliance and deviations from bleed management guidelines (as presented in Table 8 of the Protocol) will be listed and summarized descriptively.

6.9 ANTIDRUG ANTIBODY

ADA will be analyzed similarly as PD after the 1st significant dose. Number of participants testing positive for antidrug antibody (ADA) pre-study-drug (before first study drug dose in TDR14767(ALN-AT3SC-001) study) and post-study-drug administration will be summarized by Hemophilia type (A/B) and incidence of ADA positivity will be presented by frequency and as a percent by Hemophilia type and across all participants. In addition, maximum ADA titer and range of titer values will be presented by hemophilia type and across all participants, if applicable. ADA results will be listed by visit.

6.10 PRE-FILLED SYRINGE

Study drug may be provided in prefilled syringes (PFS) either at the clinic (healthcare setting) or in a non-healthcare setting (home injection) in a subset of participants receiving 80 mg monthly dose of fitusiran. In order to investigate safety and efficacy during PFS administration, data relating to exposure (for example, number of doses administered via PFS), safety (eg, related ISRs, etc) as well as ABR will be summarized descriptively for PFS usage period and vial usage period respectively under the original dose and regimen.

6.11 SUBGROUP ANALYSIS

Participants who received their significant dose in parent study will be considered as a subgroup for below endpoints. These subgroup analyses only appliable for the analyses under the original dose and regimen.

- Annualized bleeding rate (ABR) during the efficacy period for treated bleeds and all bleeds
- Annualized weight-adjusted consumption of FVIII, FIX and BPA
- Quality of life (QoL) measured by EuroQol 5-dimension 5-level (EQ-5D-5L) score
- QoL measured by Haem-A-QoL score
- AT activity level
- TG level

Negative binomial regression model will be applied only for subgroup that has at least 3 participants and the model converges. Otherwise, only summary statistics will be presented.

7 REFERENCES

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

8 APPENDIX: QUESTIONNAIRE/SCORING

8.1 HAEM-A-QOL

The Haem-A-QoL questionnaire is psychometrically tested QoL assessment instrument for participants with hemophilia and includes 46 items contributing to 10 QoL domains (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality). Scoring for each item is based on a 5-point Likert scale (never, rarely, sometimes, often, and all the time), and higher scores represent greater impairment.

Basically high score represent low quality of life and the Haem-A-QoL scoring involves the following steps:

1. For negatively worded items, assign numbers to the response scale: 1 = never, 2 = seldom, 3 = sometimes, 4 = often, 5 = all the time.
2. For positively worded items, the score has to be reversed: 1 = all the time, 2 = often, 3 = sometimes, 4 = seldom, 5 = never.
3. Use the Scoring List to identify which items belong to a subscale.
4. Summing up the items belonging to a subscale yields the raw score per subscale. Its range lies between the lowest possible (number of items (n) x 1) and highest possible (number of items (n) x 5) value of the respective scale.
5. Comparing scores across subscales is possible. If this raw score is divided by the number of items in the scale, the resulting standardized scale score can have any (also decimal) value between 1 and 5. A value of 1 represents the highest possible quality of life rating and a value of 5 the lowest possible quality of life rating of the participant.
6. Transferring a raw score to a transformed scale score between 0 and 100 makes it possible to express the scale score in percent between the lowest (0) and the highest (100) possible value. To obtain the transformed scale score (TSS) the following transformation rule has to be applied:

$$TSS = 100x\frac{raw - score - minimal - possible - raw - score(of - the - subscale)}{possible - range - of - raw - scores(of - the - subscale)}$$

Example:

A raw **score** of 11 on the "Feelings" Scale is to be transformed:

- Minimal possible raw score = 4 (since there are 4 items and lowest score for each item is 1.)
- Possible range of raw scores = maximal possible raw score – minimal possible raw score = (4 items x 5 [max score]) – 4 = 20 – 4
  = 16

TSS = 100 x (11 – 4) / 16 = 43.75

7. Producing the Total score involves the addition of the scores of a person using all items (instead of the subscale items only) of the questionnaire (again paying attention to the recoding procedure - see Steps 1 and 2). Items may be added to form a total raw score (according to Step 4, but using all items), a total standardized score (according to Step 5, but using all items) or a total transformed score (according to Step 6, but using all items).
8. If there is missing item score within a domain, the standardized scale score and transformed score for that domain will be calculated based on the number of items answered if at least 50% of those scores are non-missing and otherwise it is set to missing. Of note, participants can answer "Not applicable" to questions in the sports and leisure, work and school, and family planning domains. In this case, the domain score will be calculated if at least 50% of those scores are non-missing and not responded to "Not Applicable". The raw score for that domain will be set to missing if at least one item score is missing.

Table 1: Haem-A- QoL domains and an example item in each domain

Haem-A-QoL domains	Example items
Physical health (5 items)	In the past month, it was painful for me to move
Feelings (4 items)	In the past month, I was worried because of my haemophilia
View of yourself (5 items)	In the past month, I felt different from others because of my haemophilia
Sports & leisure (5 items)	In the past month, I had to avoid sports that I like because of my haemophilia
Work & school (4 items)	In the past month, my everyday work/school activities were jeopardized by my haemophilia
Dealing with haemophilia (3 items)	In the past month, I was able to tell whether or not I was bleeding
Treatment (8 items)	In the past month, I had problems with how my treatment was administered
Future (5 items)	In the past month, I have been thinking that it will be difficult for me to lead a normal life
Family planning (4 items)	In the past month, I have been worrying about not being able to raise a family
Partnership & sexuality (3 items)	In the past month, I haven't been able to have a normal relationship because of my haemophilia

8.2 EUROQOL-5 DIMENSION 5 LEVEL (EQ-5D-5L) SCORE

The EQ-5D-5L is a standardized instrument for use as a measure of QoL outcome. It consists of a descriptive system and a visual analog scale (VAS).

1. EQ-5D descriptive system: has 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems).
2. EQ-5D VAS: is a continuous score ranging from 0 to 100.
3. EQ-5D Valuation index: The information of the 5 dimensions of the descriptive system summarized into one index. The EQ-5D-5L index value is calculated using the crosswalk link function and the individual responses to the EQ-5D5L descriptive system.

Signature Page for VV-CLIN-0050037 v3.0
lte14762-16-1-9-sap

Approve & eSign	[redacted]
Approve & eSign	[redacted]