Clinical trial results:
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

Summary

EudraCT number	2015-001395-21
Trial protocol	GB BG
Global end of trial date	21 March 2023

Results information

Result version number	v1 (current)
This version publication date	30 March 2024
First version publication date	30 March 2024

Trial information

Trial identification

Sponsor protocol code	LTE14762

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02554773
WHO universal trial number (UTN)	U1111-1251-5204

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	450 Water Street, Cambridge, Massachusetts, United States, 02141
Public contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	34
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	34
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 13 centers in 5 countries between 18 September 2015 and 21 March 2023. A total of 34 participants were enrolled in this study.

Pre-assignment

Screening details:

Participants were rolled over from the parent study TDR14767 (NCT02035605).
SAS 1= Safety Analysis Set 1, SAS 2= Safety Analysis Set 2, and AT= Antithrombin.

Period 1

Period 1 title	Original Dose Regimen (SAS 1)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Original Dose Regimen (SAS 1)

Arm description:

Participants received fitusiran 50 milligram (mg) or 80 mg subcutaneous (SC) injection every month (QM) under the original dose and regimen.

Arm type	Experimental
Investigational medicinal product name	Fitusiran
Investigational medicinal product code	
Other name	SAR439774, ALN-AT3SC
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Fitusiran 50 mg or 80 mg SC injection was administered at the clinic (healthcare setting) or in a nonhealth care setting (home injection) QM under the original dose and regimen.

Number of subjects in period 1	Original Dose Regimen (SAS 1)
Started	34
Completed	18
Not completed	16
Physician decision	1
Consent withdrawn by subject	7
Adverse event, non-fatal	3
Death	1
Unspecified	4

Period 2	
Period 2 title	AT-Based Dose Regimen (SAS 2)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	AT-Based Dose Regimen (SAS 2)

Arm description:

Participants received fitusiran 50 mg QM, 80 mg QM or 50 mg every 2 months (Q2M) SC injection under recommended AT-based dose regimen.

Arm type	Experimental
Investigational medicinal product name	Fitusiran
Investigational medicinal product code	
Other name	SAR439774, ALN-AT3SC
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Fitusiran 50 mg QM, 80 mg QM or 50 mg Q2M SC injection was administered at the clinic (healthcare setting) or in a nonhealth care setting (home injection) under recommended AT-based dose regimen.

Number of subjects in period 2	AT-Based Dose Regimen (SAS 2)
Started	18
Completed	12
Not completed	6
Consent withdrawn by subject	1
More than 1 AT measurement <15%	1
Adverse event, non-fatal	1
Unspecified	3

Baseline characteristics

Reporting groups	
Reporting group title	Original Dose Regimen (SAS 1)
Reporting group description:	
Participants received fitusiran 50 milligram (mg) or 80 mg subcutaneous (SC) injection every month (QM) under the original dose and regimen.	

Reporting group values	Original Dose Regimen (SAS 1)	Total	
Number of subjects	34	34	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 36.6 ± 10.7	 -	
Gender categorical Units: Subjects			
Female	0	0	
Male	34	34	
Race Units: Subjects			
Caucasian/White	33	33	
Asian/Oriental	1	1	

End points reporting groups

Reporting group title	Original Dose Regimen (SAS 1)
Reporting group description:	
Participants received fitusiran 50 milligram (mg) or 80 mg subcutaneous (SC) injection every month (QM) under the original dose and regimen.	
Reporting group title	AT-Based Dose Regimen (SAS 2)
Reporting group description:	
Participants received fitusiran 50 mg QM, 80 mg QM or 50 mg every 2 months (Q2M) SC injection under recommended AT-based dose regimen.	
Subject analysis set title	Fitusiran 50 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received fitusiran 50 mg QM or Q2M SC injection under original dose regimen (SAS 1) and AT-based dose regimen (SAS 2).	
Subject analysis set title	Fitusiran 80 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received fitusiran 80 mg QM SC injection under original dose regimen (SAS 1) and AT-based dose regimen (SAS 2).	

Primary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (SAEs)[1]
End point description:	
Adverse event (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a study drug and which does not necessarily have to have a causal relationship with treatment. SAE is any untoward medical occurrence that results: death or life-threatening or inpatient hospitalization or prolongation of existing hospitalization or persistent or significant disability or congenital anomaly or medically important event. All AEs collected were considered TEAE as all participants received dose in parent study. AE of special interest (AESI) are alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations >3× upper limit of normal (ULN) or suspected or confirmed thromboembolic events or severe or serious injection site reactions or systemic injection associated reactions or cholecystitis or cholelithiasis. Results are based on safety analysis set (SAS) included all participants who received at least a partial dose of study drug.	
End point type	Primary
End point timeframe:	
From first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: participants				
Any TEAE	33	14		
Any Treatment-emergent SAE	13	1		
Any Treatment-emergent AESI	11	1		

Any TEAE leading to study drug discontinuation	5	1		
Any TEAE leading to death	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Potentially Clinically Significant Abnormality (PCSA): Hematology

End point title	Number of Participants With Potentially Clinically Significant Abnormality (PCSA): Hematology[2]

End point description:

Blood samples were collected to determine the hematology laboratory significant abnormalities. Results are based on the SAS included all participants who received at least a partial dose of study drug. Here, DFB = decrease from baseline, NB = non-black, and B = black.

End point type	Primary

End point timeframe:

From first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: participants				
Hemoglobin: <= 115 gram per liter (g/L)	5	2		
Hemoglobin: >= 185 g/L	3	1		
Hemoglobin: DFB >= 20 g/L	10	3		
Hematocrit: <= 0.37 fraction of 1	8	3		
Hematocrit: >= 0.55 fraction of 1	5	2		
Erythrocyte Count: >= 6 x 10^12/L	9	3		
Platelet Count: < 100 x 10^9/L	2	0		
Leukocyte Count: <3 x 10^9/L (NB); <2 x 10^9/L (B)	3	1		
Leukocyte Count: >= 16 x 10^9/L	1	1		
Neutrophils: <1.5 x 10^9/L (NB); <1 x 10^9/L (B)	8	2		
Lymphocytes: > 4 x 10^9/L	0	1		
Monocytes: > 0.7 x 10^9/L	15	3		
Basophils: > 0.1 x 10^9/L	4	0		
Eosinophils:>0.5x10^9/L or >ULN (ULN >=0.5x10^9/L)	11	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Potentially Clinically Significant Abnormality: Clinical Chemistry

End point title	Number of Participants With Potentially Clinically Significant Abnormality: Clinical Chemistry[3]

End point description:

Blood samples were collected to determine the clinical chemistry laboratory abnormalities. Results are based on the SAS included all participants who received at least a partial dose of study drug. Here, mmol/L = millimoles per liter, LLN = lower limit of normal, mg/L = milligram per liter, umol/L = micromoles per liter, mL/min = milliliter per minute, m^2 = meter square, CB = conjugated bilirubin, and DB = direct bilirubin.

End point type	Primary

End point timeframe:

From first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: participants				
Glucose: <= 3.9 mmol/L and < LLN	13	2		
Glucose:>=11.1 mmol/L(unfasted);>=7 mmol/L(fasted)	10	2		
C-Reactive Protein: > 2 ULN or > 10 mg/L	20	7		
Sodium: <= 129 mmol/L	1	0		
Potassium: < 3 mmol/L	2	0		
Potassium: >= 5.5 mmol/L	5	0		
Creatinine: >= 150 umol/L	1	1		
Creatinine: >= 30% change from baseline	13	7		
Creatinine: >= 100% change from baseline	2	1		
Creatinine Clearance: >= 60 - < 90 mL/min/1.73m^2	18	2		
Creatinine Clearance: >= 15 - < 30 mL/min/1.73m^2	1	1		
Uric Acid: < 120 umol/L	2	0		
Uric Acid: > 408 umol/L	20	8		
ALT: > 1 ULN	30	6		
ALT: > 3 ULN	14	1		
ALT: > 5 ULN	6	1		
ALT: > 10 ULN	2	0		
ALT: > 20 ULN	1	0		
AST: > 1 ULN	22	7		
AST: > 3 ULN	8	1		
AST: > 5 ULN	5	0		
AST: > 10 ULN	1	0		

Alkaline Phosphatase: > 1.5 ULN	4	0		
Total Bilirubin: > 1.5 ULN	4	2		
CB: DB >35% Bilirubin and Bilirubin >1.5 ULN	3	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Potentially Clinically Significant Abnormality: Urinalysis

End point title	Number of Participants With Potentially Clinically Significant Abnormality: Urinalysis[4]

End point description:

Urine samples were collected to determine the significant abnormalities in urine.

End point type	Primary

End point timeframe:

From first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: participants				

Notes:

[5] - No participants were analyzed for this endpoint.

[6] - No participants were analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Potentially Clinically Significant Abnormality: Vital Signs

End point title	Number of Participants With Potentially Clinically Significant Abnormality: Vital Signs[7]

End point description:

Participants vital signs were examined to determine the abnormalities. Vital signs included weight, supine systolic blood pressure (SSBP) and supine diastolic blood pressure (SDBP). Results are based on the SAS included all participants who received at least a partial dose of study drug. Here, mmHg = millimeter of mercury, IFB = increase from baseline, and 99999 = no participants were analyzed.

End point type	Primary

End point timeframe:

From first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: participants				
SSBP: >= 160 mmHg; IFB >= 20 mmHg	1	99999		
SDBP: <= 45 mmHg; DFB >= 20 mmHg	1	99999		
Weight: >= 5% DFB	8	3		
Weight: >= 5% IFB	15	9		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Potentially Clinically Significant Abnormality: Electrocardiogram (ECG)

End point title	Number of Participants With Potentially Clinically Significant Abnormality: Electrocardiogram (ECG)[8]

End point description:

Standard 12-lead ECGs were recorded after at least 15 minutes in the supine position using an electrocardiographic device. The following were assessed: heart rate, rhythm, interval between the peaks of successive QRS complexes (RR), interval from the beginning of the P wave until the beginning of the QRS complex (PR), interval from start of the Q wave to the end of the S wave (QRS), interval between the start of the Q wave and the end of the T wave (QT), QT interval corrected for heart rate (QTc) automatic correction evaluation, QRS axis, left ventricular hypertrophy criteria, right ventricular hypertrophy criteria, repolarization charges, and overall cardiac impression for each participant. Results are based on the SAS included all participants who received at least a partial dose of study drug. Here, msec = milliseconds and 99999 = no participants were analyzed.

End point type	Primary

End point timeframe:

From first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: participants				
Ventricular Rate: < 50 beats/min	1	99999		
Ventricular Rate: > 90 beats/min	8	5		
Ventricular Rate: >90 beats/min;IFB >=20 beats/min	3	1		
Ventricular Rate: > 100 beats/min	5	1		
Ventricular Rate:>100 beats/min;IFB >=20 beats/min	1	99999		
PR Interval: > 200 msec	3	99999		
PR Interval: > 200 msec; IFB >= 25%	2	99999		
PR Interval: > 220 msec	2	99999		

PR Interval: > 220 msec; IFB >= 25%	2	99999		
PR Interval: > 240 msec	2	99999		
PR Interval: > 240 msec;IFB >= 25%	2	99999		
QRS Interval: > 110 msec	8	3		
QRS Interval: > 110 msec; IFB >= 25%	3	99999		
QRS Interval: > 120 msec	3	2		
QRS Interval: > 120 msec; IFB >= 25%	3	99999		
QTc Bazett: > 450 msec	2	4		
QTc Bazett: > 480 msec	1	1		
QTc Bazett: IFB (30-60) msec	8	4		
QTc Fridericia: > 450 msec	1	1		
QTc Fridericia: > 480 msec	99999	1		
QTc Fridericia: IFB (30-60) msec	4	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Potentially Clinically Significant Abnormality: Physical Examination

End point title	Number of Participants With Potentially Clinically Significant Abnormality: Physical Examination[9]

End point description:

Physical examination included, at a minimum, an assessment of the participant's general appearance; skin; head, eyes, ears, nose, and throat; examinations of lymph nodes, abdomen, extremities/joints, neurological and mental status; heart and respiratory auscultation; peripheral arterial pulse; and pupil, knee, achilles, and plantar reflexes. Results are based on the SAS included all participants who received at least a partial dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: participants	17	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate (ABR) During the Efficacy Period

End point title	Annualized Bleeding Rate (ABR) During the Efficacy Period

End point description:

The ABR was annualized for each participant using the following formula: ABR = total number of bleeding events/total number of days in the respective period x 365.25. The efficacy period was 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 for full analysis set 1 and the dose re-start Day 169 to the end of study visit for full analysis set 2. Results are based on the full analysis set (FAS) included all participants in SAS.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: bleeding events per year				
number (confidence interval 95%)	3.035 (1.845 to 4.992)	3.929 (1.622 to 9.520)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Spontaneous Bleeding Rate During the Efficacy Period

End point title	Annualized Spontaneous Bleeding Rate During the Efficacy Period

End point description:

A spontaneous bleeding episode was defined as a bleeding event that occurred for no apparent or known reason, particularly into the joints, muscles, and soft tissues. The efficacy period was 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 for full analysis set 1 and the dose re-start Day 169 to the end of study visit for full analysis set 2. Results are based on the FAS included all participants in SAS.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: bleeding events per year				
arithmetic mean (standard deviation)	2.60 (± 5.96)	3.96 (± 11.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Joint Bleeding Rate During the Efficacy Period

End point title	Annualized Joint Bleeding Rate During the Efficacy Period

End point description:

A joint bleeding episode was defined as an event that 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. The efficacy period was 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 for full analysis set 1 and the dose re-start Day 169 to the end of study visit for full analysis set 2. Results are based on the FAS included all participants in SAS.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: bleeding events per year				
arithmetic mean (standard deviation)	3.51 (± 6.97)	4.78 (± 11.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time Intervals Between Bleeding Events

End point title	Time Intervals Between Bleeding Events

End point description:

Bleed-free duration was defined as the time interval between 2 protocol-defined treated bleeding events, excluding events that occurred during the intercurrent periods. Results are based on the FAS included all participants in SAS.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: days				
median (full range (min-max))	368.50 (56.0 to 1576.0)	249.00 (11.0 to 427.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Weight-Adjusted Consumption of Coagulation Factor VIII (FVIII) and Coagulation Factor IX (FIX)

End point title	Annualized Weight-Adjusted Consumption of Coagulation Factor VIII (FVIII) and Coagulation Factor IX (FIX)

End point description:

Number of coagulation factor injections per bleed, weight-adjusted total dose per injection and total dose per bleed was determined. Results are based on the FAS included all participants in SAS. Here, n = number of participants analyzed for each factor.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	18		
Units: international units per kilogram (kg)				
arithmetic mean (standard deviation)				
FVIII (n= 11, 3)	63.66 (± 81.29)	52.13 (± 8.50)		
FIXs (n= 5, 3)	110.26 (± 93.74)	108.63 (± 138.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Weight-Adjusted Consumption of Bypassing Agent (BPA) of Recombinant Factor VIIa (rFVIIa)

End point title	Annualized Weight-Adjusted Consumption of Bypassing Agent (BPA) of Recombinant Factor VIIa (rFVIIa)

End point description:

Number of BPA injections per bleed, weight-adjusted total dose per injection and total dose per bleed

was determined. Results are based on the FAS included all participants in SAS. Only participants analyzed for this endpoint are reported.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: microgram/kg				
arithmetic mean (standard deviation)	1316.19 (± 2631.87)	1431.84 (± 2369.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Weight-Adjusted Consumption of Bypassing Agent (BPA) of Activated Prothrombin Complex Concentrate (aPCC)

End point title	Annualized Weight-Adjusted Consumption of Bypassing Agent (BPA) of Activated Prothrombin Complex Concentrate (aPCC)

End point description:

Number of BPA injections per bleed, weight-adjusted total dose per injection and total dose per bleed was determined. Results are based on the FAS included all participants in SAS. Only participants analyzed for this endpoint are reported.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1

End point values	Original Dose Regimen (SAS 1)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: units/kg				
arithmetic mean (standard deviation)	381.81 (± 409.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL 5-Dimension 5-level Questionnaire (EQ-5D-5L) Index and Visual Analog Scale (VAS) Scores at Month 24

End point title	Change From Baseline in EuroQoL 5-Dimension 5-level Questionnaire (EQ-5D-5L) Index and Visual Analog Scale (VAS) Scores at Month 24

End point description:

The EQ-5D-5L is a standardized and disease-generic instrument for use as a measure of quality of life (QoL) outcome. It consists of a questionnaire pertaining to 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS. The 5 dimensions questionnaire is based on 5 degrees of severity (1= no problems, 2= slight problems, 3= moderate problems, 4= severe problems, or 5= extreme problems). The EQ-5D-5L index value was calculated using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system. The VAS is a continuous score ranging from 0 to 100. Lower score indicated improvement in QoL. Baseline refers to the last non-missing value on or before the first significant treatment in TDR14767(ALN-AT3SC-001) or LTE14762 study. Results are based on the FAS included all participants in SAS. Only participants analyzed at baseline and Month 24 are reported.

End point type	Secondary

End point timeframe:

Baseline and Month 24

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	3		
Units: units on a scale				
arithmetic mean (standard deviation)				
Index score	0.01 (± 0.14)	0.09 (± 0.06)		
VAS score	4.73 (± 18.37)	16.67 (± 7.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Haemophilia Quality of Life Questionnaire (Haem-A-QoL) Total Score and Physical Health Scores at Month 24

End point title	Change From Baseline in Haemophilia Quality of Life Questionnaire (Haem-A-QoL) Total Score and Physical Health Scores at Month 24

End point description:

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 (1= never, 2= rarely, 3= sometimes, 4= often, and 5= all the time), and the physical health and total transformed scores range from 0 to 100. Higher scores indicated greater impairment. Baseline refers to the last non-missing value on or before the first significant treatment in TDR14767(ALN-AT3SC-001) or LTE14762 study. Results are based on the FAS included all participants in SAS. Only participants analyzed at baseline and Month 24 are reported.

End point type	Secondary

End point timeframe:

Baseline and Month 24

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	3		
Units: units on a scale				
arithmetic mean (standard deviation)				
Total score	-0.20 (± 0.47)	0.02 (± 0.34)		
Physical health score	-0.14 (± 0.58)	-0.53 (± 0.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antithrombin Activity Level Over Time

End point title	Antithrombin Activity Level Over Time

End point description:

The AT activity level was analyzed at each post-baseline visit. The baseline under the original dose and regimen was the last non-missing assessment before the first significant dose. Results are based on the Pharmacodynamic (PD) analysis set included all participants who received at least 1 dose of study drug and had at least 1 blood sample collection post dose to determine plasma AT and thrombin generation (TG) levels.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: percentage of antithrombin				
arithmetic mean (standard deviation)	16.28 (± 4.53)	24.76 (± 7.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Thrombin Generation Over Time

End point title	Thrombin Generation Over Time

End point description:

The TG data was analyzed by CoagScope and assay performed using calibrated automated thrombogram method. The baseline under the original dose and regimen was the last non-missing

assessment before the first significant dose. Results are based on the PD analysis set included all participants who received at least 1 dose of study drug and had at least 1 blood sample collection post dose to determine plasma AT and TG levels.

End point type	Secondary

End point timeframe:

From Day 29 up to end of treatment regimen in SAS 1 and SAS 2

End point values	Original Dose Regimen (SAS 1)	AT-Based Dose Regimen (SAS 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: nanomoles/liter				
arithmetic mean (standard deviation)	71.39 (± 24.67)	32.31 (± 20.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Fitusiran

End point title	Maximum Observed Concentration (Cmax) of Fitusiran

End point description:

Cmax was defined as maximum plasma concentration observed. The non-compartmental Pharmacokinetic (PK) analysis was performed. Results are based on the Pharmacokinetic (PK) analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Here, n = number of participants analyzed at each specific time point.

End point type	Secondary

End point timeframe:

At Day 1, Months 12 and 24

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1 (n= 14, 17)	86.8 (± 44.1)	168 (± 74.6)		
Month 12 (n= 9, 10)	75.2 (± 50.3)	149 (± 53.2)		
Month 24 (n= 2, 9)	62.5 (± 35.3)	155 (± 87.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach the Maximum Concentration (tmax) of Fitusiran

End point title	Time to Reach the Maximum Concentration (tmax) of Fitusiran

End point description:

tmax was defined as time to reach Cmax. The non-compartmental PK analysis was performed. Results are based on the PK analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Here, n = number of participants analyzed at each specific time point.

End point type	Secondary

End point timeframe:

At Day 1, Months 12 and 24

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: hour				
median (full range (min-max))				
Day 1 (n= 14, 17)	3.97 (0.50 to 8.08)	4.00 (2.00 to 8.07)		
Month 12 (n= 9, 10)	4.02 (2.00 to 8.00)	6.00 (2.02 to 8.03)		
Month 24 (n= 2, 9)	4.00 (4.00 to 4.00)	7.83 (4.05 to 8.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve From Time 0 to the Real Time (AUClast) of Fitusiran

End point title	Area Under the Concentration Versus Time Curve From Time 0 to the Real Time (AUClast) of Fitusiran

End point description:

AUClast was defined as area under the concentration versus time curve from time 0 to the last measurable concentration. The non-compartmental PK analysis was performed. Results are based on the PK analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Here, n = number of participants analyzed at each specific time point.

End point type	Secondary

End point timeframe:

At Day 1, Months 12 and 24

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: ng*hour/mL				
arithmetic mean (standard deviation)				
Day 1 (n= 14, 17)	1110 (± 486)	2130 (± 769)		
Month 12 (n= 9, 10)	961 (± 551)	2020 (± 708)		
Month 24 (n= 2, 9)	935 (± 550)	2070 (± 917)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve Extrapolated to Infinity (AUCinf) of Fitusiran

End point title	Area Under the Concentration Versus Time Curve Extrapolated to Infinity (AUCinf) of Fitusiran

End point description:

AUCinf was defined as area under the concentration versus time curve extrapolated to infinity. The non-compartmental PK analysis was performed. Results are based on the PK analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Here, n = number of participants analyzed at each specific time point and 99999 = standard deviation could not be determined when only 1 participant was analyzed.

End point type	Secondary

End point timeframe:

At Day 1 and Month 12

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Day 1 (n= 4, 3)	1470 (± 441)	2230 (± 641)		
Month 12 (n= 1, 1)	356 (± 99999)	2860 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-Life (t1/2z) of Fitusiran

End point title	Terminal Half-Life (t1/2z) of Fitusiran

End point description:

t1/2z associated with the terminal slope (λz) determined according to the following equation: t1/2z =

0.693/λz; where, λz is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semi-logarithmic scale. The non-compartmental PK analysis was performed. Results are based on the PK analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Here, n = number of participants analyzed at each specific time point and 99999 = standard deviation could not be determined when only 1 participant was analyzed.

End point type	Secondary

End point timeframe:

At Day 1 and Month 12

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: hour				
arithmetic mean (standard deviation)				
Day 1 (n= 5, 3)	5.19 (± 1.61)	5.90 (± 3.83)		
Month 12 (n= 1, 1)	3.91 (± 99999)	4.94 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Body Clearance (CL/F) of Fitusiran

End point title	Apparent Total Body Clearance (CL/F) of Fitusiran

End point description:

CL/F was defined as apparent clearance of study drug from the body. The non-compartmental PK analysis was performed. Results are based on the PK analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Here, n = number of participants analyzed at each specific time point and 99999 = standard deviation could not be determined when only 1 participant was analyzed.

End point type	Secondary

End point timeframe:

At Day 1 and Month 12

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: liter per hour				
arithmetic mean (standard deviation)				
Day 1 (n= 4, 3)	37.6 (± 13.6)	38.8 (± 12.7)		
Month 12 (n= 1, 1)	143 (± 99999)	28.3 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution at the Steady State After Single Extravascular Dose (Vss/F) of Fitusiran

End point title	Apparent Volume of Distribution at the Steady State After Single Extravascular Dose (Vss/F) of Fitusiran

End point description:

Vss/F was defined as apparent volume of distribution of study drug at steady state concentration. The non-compartmental PK analysis was performed. Results are based on the PK analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Here, n = number of participants analyzed at each specific time point and 99999 = standard deviation could not be determined when only 1 participant was analyzed.

End point type	Secondary

End point timeframe:

At Day 1 and Month 12

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: liter				
arithmetic mean (standard deviation)				
Day 1 (n= 4, 3)	283 (± 155)	390 (± 348)		
Month 12 (n= 1, 1)	834 (± 99999)	204 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Recovery of Fraction of the Dose Excreted in Urine (fe) in 0-24 Hours After Fitusiran Administration

End point title	Recovery of Fraction of the Dose Excreted in Urine (fe) in 0-24 Hours After Fitusiran Administration

End point description:

fe was defined as the amount of fitusiran excreted in urine in 0-24 hour. The non-compartmental PK analysis was performed. Results are based on the PK analysis set included all participants who received at least 1 dose of study drug and have at least 1 blood sample collection post dose to determine plasma concentrations of study drug. Only those participants with data available at Month 24 were reported.

End point type	Secondary

End point timeframe:

Postdose, 0 to 6 hours, 6 to 12 hours, 12 to 24 hours at Month 24

End point values	Fitusiran 50 mg	Fitusiran 80 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	7		
Units: percentage of study drug				
arithmetic mean (standard deviation)	10.7 (± 4.08)	12.6 (± 4.92)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
TEAEs data was collected from first dose of study drug (Day 1) up to end of treatment regimen in SAS 1 and SAS 2.	
Adverse event reporting additional description:	
Analysis was performed on the safety analysis set.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	AT-Based Dose Regimen (SAS 2)
Reporting group description:	
Participants received fitusiran 50 mg QM, 80 mg QM or 50 mg Q2M SC injection under recommended AT-based dose regimen.	
Reporting group title	Original Dose Regimen (SAS 1)
Reporting group description:	
Participants received fitusiran 50 mg or 80 mg SC injection QM under the original dose and regimen.	

Serious adverse events	AT-Based Dose Regimen (SAS 2)	Original Dose Regimen (SAS 1)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	13 / 34 (38.24%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Transaminases Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular Carcinoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia Postoperative			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Thrombosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal Ulcer			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Erosive Gastritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic Ulcer Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilic Arthropathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AT-Based Dose Regimen (SAS 2)	Original Dose Regimen (SAS 1)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	33 / 34 (97.06%)	
Vascular disorders			
Brachiocephalic Vein Stenosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Collateral Circulation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	

Superficial Vein Thrombosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Essential Hypertension			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Hypertension			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Phlebitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Asthenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Chest Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Injection Site Atrophy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Influenza Like Illness			
subjects affected / exposed	0 / 18 (0.00%)	4 / 34 (11.76%)	
occurrences (all)	0	5	
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Injection Site Discolouration			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Injection Site Pain			

subjects affected / exposed	0 / 18 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Injection Site Haematoma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Injection Site Erythema			
subjects affected / exposed	0 / 18 (0.00%)	7 / 34 (20.59%)	
occurrences (all)	0	40	
Injection Site Swelling			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	7	
Peripheral Swelling			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Swelling Face			
subjects affected / exposed	1 / 18 (5.56%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Immune system disorders			
Allergy To Animal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Seasonal Allergy			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Social circumstances			
Tattoo			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pregnancy Of Partner			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Testicular Mass			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Testicular Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Bronchitis Chronic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Asthma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Nasal Septum Deviation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Oropharyngeal Pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	8	
Productive Cough			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 18 (0.00%)	4 / 34 (11.76%)	
occurrences (all)	0	6	
Dyspnoea			

subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Nasal Congestion			
subjects affected / exposed	0 / 18 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Nasal Obstruction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rhinitis Allergic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitated Depression			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Investigations			
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 18 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 18 (0.00%)	10 / 34 (29.41%)	
occurrences (all)	0	15	
C-Reactive Protein Increased			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Haematocrit Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Gamma-Glutamyltransferase Increased			

subjects affected / exposed	0 / 18 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Fibrin D Dimer Increased			
subjects affected / exposed	1 / 18 (5.56%)	3 / 34 (8.82%)	
occurrences (all)	1	3	
Haemoglobin Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Prostatic Specific Antigen Increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Protein Urine Present			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Prothrombin Fragment 1.2 Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Red Blood Cell Count Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Transaminases Increased			
subjects affected / exposed	1 / 18 (5.56%)	5 / 34 (14.71%)	
occurrences (all)	1	9	
Vitamin D Decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Weight Decreased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Weight Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Anaemia Postoperative			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Arthropod Bite			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hyphaema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Foot Fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Joint Injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Ligament Sprain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Limb Injury			
subjects affected / exposed	1 / 18 (5.56%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Muscle Strain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Paternal Exposure Before Pregnancy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Post Procedural Erythema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Post Procedural Oedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Road Traffic Accident			

subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Procedural Pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Post Procedural Swelling			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Thermal Burn			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Cardiac disorders			
Bundle Branch Block Right			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nervous system disorders			
Cerebral Cyst			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 18 (5.56%)	9 / 34 (26.47%)	
occurrences (all)	1	21	
Hypoaesthesia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypogeusia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Syncope			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Blood Loss Anaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	6	
Neutropenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis Allergic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Retinopathy Hypertensive			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Eye Inflammation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Erythema Of Eyelid			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Swelling Of Eyelid			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Visual Impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Abdominal Distension			

subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Abdominal Pain			
subjects affected / exposed	0 / 18 (0.00%)	4 / 34 (11.76%)	
occurrences (all)	0	5	
Abdominal Tenderness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Abdominal Pain Upper			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	4	
Abdominal Pain Lower			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Anal Fissure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 18 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	4	
Colitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Dental Caries			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Diverticulum Intestinal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)	6 / 34 (17.65%)	
occurrences (all)	0	6	
Faeces Pale			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	4	
Duodenal Ulcer			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Epigastric Discomfort			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	5	
Gastritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Gastric Ulcer			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Food Poisoning			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Gastritis Erosive			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Femoral Hernia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Periodontal Disease			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 18 (0.00%)	4 / 34 (11.76%)	
occurrences (all)	0	7	
Toothache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed	0 / 18 (0.00%)	4 / 34 (11.76%)	
occurrences (all)	0	4	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Cholecystitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Keratosis Pilaris			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Palmar Erythema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Ingrowing Nail			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hangnail			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Erythema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rash			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rash Erythematous			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Rash Pruritic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Dysuria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Chronic Kidney Disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Calculus Urinary			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 18 (5.56%)	8 / 34 (23.53%)	
occurrences (all)	1	15	
Arthritis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Back Pain			
subjects affected / exposed	0 / 18 (0.00%)	6 / 34 (17.65%)	
occurrences (all)	0	10	
Joint Swelling			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Joint Range Of Motion Decreased			

subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Haemophilic Arthropathy			
subjects affected / exposed	0 / 18 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	4	
Medial Tibial Stress Syndrome			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Muscle Tightness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Neck Pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Musculoskeletal Discomfort			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Pain In Extremity			
subjects affected / exposed	1 / 18 (5.56%)	4 / 34 (11.76%)	
occurrences (all)	1	5	
Synovial Cyst			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Sacral Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Synovitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Tendon Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Infections and infestations			

Asymptomatic Covid-19			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Herpes Dermatitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Helicobacter Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Ear Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Covid-19			
subjects affected / exposed	2 / 18 (11.11%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Nail Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	7 / 34 (20.59%)	
occurrences (all)	1	13	
Oral Candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	4	

Otitis Media			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Periodontitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Tonsillitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Tooth Abscess			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Tooth Infection			
subjects affected / exposed	1 / 18 (5.56%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 18 (11.11%)	3 / 34 (8.82%)	
occurrences (all)	2	7	
Viral Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 18 (5.56%)	6 / 34 (17.65%)	
occurrences (all)	1	8	
Tracheitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Glucose Tolerance Impaired			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Impaired Fasting Glucose			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Vitamin D Deficiency			
subjects affected / exposed	0 / 18 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2015	• Primary changes: Exclusion criterion #3, updated to permit enrollment of participants 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 participants without inhibitors and added for participants with inhibitors; Participants 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 (TDR14767 [ALN-AT3SC-001]) to be safe and well tolerated; Addition of the Haem-A-QoL to assess QoL; Addition of text based on Ethics Committee feedback; Clarification of overlapping study assessments (vs parent study).
20 October 2016	• Primary changes: Exploratory objective added for assessment of safety and hemostatic efficacy rating for operative procedures conducted in participants 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; Participant 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.
13 June 2017	• Primary changes: Text and table added for liver function test monitoring in participants with elevated ALT; Text added to permit direct-acting antiviral treatment for Hepatitis C virus (HCV) infected participants; FibroScan (FibroTest and aspartate aminotransferase to platelet ratio index where FibroScan unavailable) added to assess liver fibrosis/cirrhosis in HCV infected participants; 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.

09 November 2017	• Primary changes: Updated clinical development status text to account for a participant death, which was reported in a participant with cerebral venous sinus thrombosis 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 Participant 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 participants who present to the study site for management of bleed symptoms, samples were 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.
31 May 2018	• Clinical development and commercialization of fitusiran were granted from Alnylam Pharmaceuticals, Inc. to Genzyme Corporation, a Sanofi Company that assumed 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 had 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' had been created or updated to reflect the Sanofi Genzyme environment.
05 March 2019	• Study extension beyond 48 months: LTE14762 was an open label extension study of the long-term safety and efficacy of fitusiran in participants with hemophilia A or B, with or without inhibitory antibodies to factor VIII or IX. The primary objective of this study was the safety and tolerability assessed by incidence, severity, relatedness, and seriousness of adverse events, and laboratory assessments. This amendment, as study duration extension, was enabled participants who had 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 provided in prefilled syringes either at the clinic or in a nonhealth care setting in a subset of participants receiving 80 mg monthly dose of fitusiran. The participant was trained on prefilled syringe self-administration. Participants who had 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 were adjusted with reducing frequency of routine clinical hematology/biochemistry and urinary laboratory evaluations, coagulation testing and exploratory biomarkers. The study duration of all participants 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 participant's safety beyond 2 years. This justifies the proposed visits and routine assessments frequency adjustment and was also reduce participant burden without compromising safety monitoring.

25 November 2020	• The main purpose of this amendment was to introduce a risk mitigation strategy for vascular thrombotic events in participants 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 were newly identified risks of fitusiran. As such, cholecystitis and cholelithiasis had been added to the protocol as AESIs. • The amendment also included 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 coronavirus disease 2019 pandemic. The guidance provided instruction on how to ensure continued dosing, monitor participants and perform assessments remotely when study participants were unable to travel to the site.
08 December 2020	• The main purpose of this amendment was to minimize the time between 2 AT measurements if the first AT result is <15%.
23 June 2021	• Antithrombin activity level was recently identified as a modifiable target for risk mitigation of vascular thrombosis in participants 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 was to extend the study duration for some participants to allow all participants currently in the study to have at least an 18 calendar months period after introduction of the revised dose and regimen (regardless of whether the individual participant changed regimen) for purposes of collecting sufficient data for assessment of efficacy and safety of the revised dose and regimen. The study duration was extended for few participants 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) was not be impacted, and the extension was concern only some participants (those who would have completed the study before having this additional follow-up).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 September 2017	US FDA clinical hold.	15 December 2017
01 October 2020	Global voluntary dosing pause due to dosing revision by the Sponsor.	01 December 2020

Notes:

Limitations and caveats

None reported