Clinical trial results:
ATLAS-PPX trial: An open-label, Multinational, Switching Study to Describe the Efficacy and Safety of Fitusiran Prophylaxis in Hemophilia A and B Patients Previously Receiving Factor or Bypassing Agent Prophylaxis

Summary

EudraCT number	2016-004087-19
Trial protocol	ES IE GB DE DK NL IT Outside EU/EEA
Global end of trial date	25 March 2022

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	EFC15110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03549871
WHO universal trial number (UTN)	U1111-1217-3270
Other trial identifiers	Alnylam: ALN-AT3SC-009

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation, A Sanofi company
Sponsor organisation address	50 Binney Street, Cambridge, MA, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001855-PIP01-15
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	27 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adolescent and adult subjects. The parent(s) or guardian(s), as well as the subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in age-appropriate language was provided and explained to the subject. Repeated invasive procedures were minimised. A topical anesthesia might have been used to minimise distress and discomfort. Adult 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	25 July 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	China: 1
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	Turkey: 34

Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Mexico: 4
Worldwide total number of subjects	80
EEA total number of subjects	7

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	23
Adults (18-64 years)	56
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 35 active sites in 15 countries. Total of 99 subjects were screened from 25 July 2018 to 19 March 2021, of which 19 were screen failure due to not meeting eligibility criteria. Study had 2 main periods: 6-month factor/BPA prophylaxis period & 7-month fitusiran treatment period (1-month onset and 6-month fitusiran efficacy).

Pre-assignment

Screening details:

Subjects with inadequate response to BPA treatment (historical annualised bleeding rate [ABR] greater than or equal to [>=] 20) prior to enrollment did not participate in 6-month prophylaxis period and they entered directly into fitusiran treatment period and were referred as 'Subgroup of Cohort A' for analysis purpose.

Period 1

Period 1 title	Factor/BPA prophylaxis period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Cohort A: Inhibitor

Arm description:

Subjects with hemophilia A or B, with inhibitory antibodies to coagulation factor VIII (FVIII) or coagulation factor IX (FIX) and who were receiving BPA prophylaxis were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with BPAs. This period was skipped by a subgroup of Cohort A which included subjects with hemophilia B with inhibitory antibodies to FIX who had not responded adequately to BPA prophylaxis prior to study entry (historical ABR >=20).

Arm type	Active comparator
Investigational medicinal product name	BPA prophylaxis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were to continue to receive BPA prophylaxis on a regimen consistent with recommendations in the approved prescribing information, allowed for adjustment to individual subject response and designed to decrease spontaneous bleeding. The regimen had to have a minimum frequency per protocol: twice weekly (activated prothrombin complex concentrates [aPCC]) or every other day (recombinant factor VIIa [rFVIIa]).

Arm title	Cohort B: Non-inhibitor

Arm description:

Subjects with hemophilia A or B, without inhibitory antibodies to FVIII or FIX who were receiving factor prophylaxis were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with factor concentrates.

Arm type	Active comparator
Investigational medicinal product name	Factor (FVIII or FIX) Prophylaxis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were to continue to receive factor concentrate prophylaxis on a regimen consistent with recommendations in the approved prescribing information, allowed for adjustment to individual subject response and designed to decrease spontaneous bleeding. The regimen had to have a minimum frequency per protocol: twice weekly (standard half-life FVIII), once weekly (extended half-life FVIII; standard half-life FIX), once biweekly (extended half-life FIX).

Number of subjects in period 1	Cohort A: Inhibitor	Cohort B: Non-inhibitor
Started	28	50
Completed	21	46
Not completed	7	4
Consent withdrawn by subject	1	2
Adverse event	1	-
Unspecified	5	2

Period 2

Period 2 title	Fitusiran Treatment period
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: Inhibitor

Arm description:

Post completion of BPA prophylaxis period, subjects entered into the 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive BPA prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. A subgroup of Cohort A (hemophilia B subjects with inhibitory antibodies to Factor IX who were not responding adequately to BPA prophylaxis prior to study entry (historical ABR >=20) entered directly into fitusiran treatment period. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate.

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

Dosage and administration details:

Fitusiran 80 milligrams (mg) once monthly (QM) as subcutaneous (SC) injection for 7 months until the sponsor initiated a voluntary dose pause. Fitusiran 50 mg once every other month (Q2M) as SC injection after dose pause and protocol amendment.

Arm title	Cohort B: Non-inhibitor

Arm description:

Post completion of factor prophylaxis period, subjects entered in to 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive their factor prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with factor, as appropriate.

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

Dosage and administration details:

Fitusiran 80 mg QM as SC injection until the sponsor initiated a voluntary dose pause. Fitusiran 50 mg Q2M as SC injection after dose pause and protocol amendment.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 as Baseline period because it included all subjects of efficacy analysis set (included the Cohort A subgroup subjects who entered directly into the fitusiran treatment period).

Number of subjects in period 2[2]	Cohort A: Inhibitor	Cohort B: Non-inhibitor
Started	23	46
80mg QM & part of safety analysis set 1	21	46
50 mg Q2M & part of safety analysis set2	2 [3]	0 [4]
Efficacy Set 1	19	46
Efficacy Set 2	2 [5]	0 [6]
Completed	17	37
Not completed	6	9
Consent withdrawn by subject	1	-
Study drug on hold	4	5
More than 1 antithrombin measurement less than 15%	1	-
Subject’s decision	-	2
Adverse event	-	2

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The baseline period (Period 2) included all completed subjects from BPA/factor prophylaxis period + 2 subjects from Cohort A subgroup who directly enrolled to fitusiran treatment period.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Received fitusiran 50mg Q2M dosing regimen after dose pause and protocol amendment 5, dated 25-Nov-2020. They were considered as safety analysis set 2 (SAS 2) and were subjected only to safety analysis and not to main efficacy analysis.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This milestone is applicable only to arm Cohort A: Inhibitor.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Efficacy Analysis Set 2 (EAS 2) included all subjects in the SAS 2 who received factor or BPA prophylaxis and any dose of fitusiran 50 mg Q2M after dose pause, protocol amendment 5 (dated 25-Nov-2020) and dose resumption.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This milestone is applicable only to arm Cohort A: Inhibitor.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: Inhibitor
Reporting group description:	
Post completion of BPA prophylaxis period, subjects entered into the 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive BPA prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. A subgroup of Cohort A (hemophilia B subjects with inhibitory antibodies to Factor IX who were not responding adequately to BPA prophylaxis prior to study entry (historical ABR >=20) entered directly into fitusiran treatment period. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate.	
Reporting group title	Cohort B: Non-inhibitor
Reporting group description:	
Post completion of factor prophylaxis period, subjects entered in to 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive their factor prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with factor, as appropriate.	

Reporting group values	Cohort A: Inhibitor	Cohort B: Non-inhibitor	Total
Number of subjects	23	46	69
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	27.7	23.5	
standard deviation	± 15.9	± 7.3	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	23	46	69
Race Units: Subjects			
White	18	27	45
Black or African American	1	0	1
Asian	4	17	21
Other	0	2	2

End points

End points reporting groups

Reporting group title	Cohort A: Inhibitor

Reporting group description:

Subjects with hemophilia A or B, with inhibitory antibodies to coagulation factor VIII (FVIII) or coagulation factor IX (FIX) and who were receiving BPA prophylaxis were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with BPAs. This period was skipped by a subgroup of Cohort A which included subjects with hemophilia B with inhibitory antibodies to FIX who had not responded adequately to BPA prophylaxis prior to study entry (historical ABR >=20).

Reporting group title	Cohort B: Non-inhibitor

Reporting group description:

Subjects with hemophilia A or B, without inhibitory antibodies to FVIII or FIX who were receiving factor prophylaxis were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with factor concentrates.

Reporting group title	Cohort A: Inhibitor

Reporting group description:

Post completion of BPA prophylaxis period, subjects entered into the 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive BPA prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. A subgroup of Cohort A (hemophilia B subjects with inhibitory antibodies to Factor IX who were not responding adequately to BPA prophylaxis prior to study entry (historical ABR >=20) entered directly into fitusiran treatment period. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate.

Reporting group title	Cohort B: Non-inhibitor

Reporting group description:

Post completion of factor prophylaxis period, subjects entered in to 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive their factor prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with factor, as appropriate.

Subject analysis set title	Overall Factor/BPA Prophylaxis Period
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects, whether with inhibitory antibodies (Cohort A) or without inhibitory antibodies (Cohort B) to FVIII or FIX and who were receiving BPA or factor prophylaxis were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study regularly scheduled prophylaxis regimen with BPAs or factors in 6-month factor or BPA prophylaxis period. This period was skipped by a subgroup of Cohort A which included subjects with hemophilia B with inhibitory antibodies to FIX and who had not responded adequately to BPA prophylaxis prior to study entry (historical ABR >=20).

Subject analysis set title	Overall Fitusiran 80 mg Efficacy Period
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received fitusiran 80 mg QM (either in Cohort A or Cohort B) until sponsor initiated a voluntary dose pause during fitusiran efficacy period (i.e., from Day 29 to Day 190 of fitusiran treatment period) and were considered for efficacy analysis during fitusiran efficacy period.

Subject analysis set title	Overall Fitusiran 80 mg Treatment Period
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received fitusiran 80 mg QM (either in Cohort A or Cohort B) until sponsor initiated a voluntary dose pause during fitusiran treatment period (i.e., 1-month onset period + 6-month efficacy period) and were considered for efficacy analysis during fitusiran treatment period.

Subject analysis set title	Overall Fitusiran 80 mg 1-Month Onset Period
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received fitusiran 80 mg QM (either in Cohort A or Cohort B) until sponsor initiated a voluntary dose pause during fitusiran 1-month onset period (i.e., from Day 1 to Day 28 of fitusiran treatment period) and were considered for the efficacy analysis during fitusiran 1-month onset period.

Subject analysis set title	BPA Prophylaxis: Cohort: A Inhibitor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with hemophilia A or B, with inhibitory antibodies to FVIII or FIX and who were receiving BPA prophylaxis were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with BPAs. This period was skipped by a subgroup of Cohort A which included subjects with hemophilia B with inhibitory antibodies to FIX who had not responded adequately to BPA prophylaxis prior to study entry (historical ABR >=20).

Subject analysis set title	Fitusiran 80 mg Prophylaxis: Cohort A: Inhibitor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Post completion of BPA prophylaxis period, subjects entered into the 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive BPA prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. A subgroup of Cohort A (hemophilia B subjects with inhibitory antibodies to Factor IX who were not responding adequately to BPA prophylaxis prior to study entry: historical ABR >=20) entered directly into fitusiran treatment period. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate.

Subject analysis set title	Factor Prophylaxis: Cohort B: Non-inhibitor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with hemophilia A or B, without inhibitory antibodies to FVIII or FIX who were receiving factor prophylaxis were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with factor concentrates.

Subject analysis set title	Fitusiran 80 mg Prophylaxis: Cohort B: Non-inhibitor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Post completion of factor prophylaxis period, subjects entered in to 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period). Subjects could continue to receive their factor prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. Throughout the study, subjects in the fitusiran treatment period could receive on-demand treatment for breakthrough bleeding episodes with factor, as appropriate.

Primary: Estimated Annualised Bleeding Rate (ABR)

End point title	Estimated Annualised Bleeding Rate (ABR)

End point description:

Bleeding episodes (BE): any occurrence of hemorrhage might require administration of factor/BPA. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location occurred within 72 hours of last injection used to treat BE at that location was considered part of original BE and counted as 1 BE towards ABR. Bleeding began after 72 hours of last injection at that location was considered as a new event. ABR = total number of qualifying BE/total number of days in the respective period*365.25. Analysis was performed on efficacy analysis set 1 (EAS1) which included subjects who received factor/BPA prophylaxis and any dose of fitusiran before dose resumption. Estimated data were derived by using repeated measures negative (NB) binomial regression model. Data collection and analysis of combined population (Cohort A & B) for each period was planned and performed for this endpoint.

End point type	Primary

End point timeframe:

Factor/BPA prophylaxis period: from Day -168 to Day -1; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Efficacy Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	65		
Units: episodes per subject per year				
number (confidence interval 95%)	7.482 (5.520 to 10.141)	2.908 (1.727 to 4.898)		

Statistical analyses

Statistical analysis title	Factor/BPA Prophylaxis vs Fitusiran 80 mg Efficacy

Statistical analysis description:

Analysed using repeated measures NB model with fixed effect of treatment period (fitusiran efficacy period or factor/BPA prophylaxis period) and robust sandwich covariance matrix was constructed to account for within subject dependence, logarithm of duration (in years) that each subject spends in each study period matching BE data being analysed as an offset variable. Number of subjects included in this analysis was 65 and not 130.

Comparison groups	Overall Fitusiran 80 mg Efficacy Period v Overall Factor/BPA Prophylaxis Period
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [1]
Method	Repeated measures NB regression model
Parameter estimate	ABR ratio
Point estimate	0.389
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.224
upper limit	0.675

Notes:

[1] - The threshold for significance was <0.05.

Primary: Observed Annualised Bleeding Rate (ABR)

End point title	Observed Annualised Bleeding Rate (ABR)[2]

End point description:

A bleeding episode (BE): any occurrence of hemorrhage might require administration of factor/BPA. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered a part of original BE and counted as 1 BE towards ABR. Any bleeding that began after 72 hours of last injection at that location was considered as a new event. ABR = total number of qualifying BE/number of days in the respective period *365.25. Analysis was performed on EAS1 population. Data collection and analysis of combined population (Cohort A and B) for each period was planned and performed for this endpoint.

End point type	Primary

End point timeframe:

Factor/BPA prophylaxis period: from Day -168 to Day -1; 6-month fitusiran efficacy period: from Day 29

to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

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 was descriptive in nature, no statistical analysis was provided.

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Efficacy Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	65		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	7.56 (± 9.49)	3.19 (± 7.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Spontaneous Bleeding Rate

End point title	Estimated Annualised Spontaneous Bleeding Rate

End point description:

BE: any occurrence of hemorrhage that might require administration of factor/BPA infusion. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered part of original BE and counted as 1 BE towards ABR. Bleeding began after 72 hours of last injection at that location was considered as a new event. Spontaneous BE: BE occurrence for no apparent/known reason, particularly into joints, muscles and soft tissues. ABR = total number of qualifying BE/number of days in respective period *365.25. Analysis was performed on EAS 1 population. Estimated data was derived using repeated measures NB regression model. Data collection and combined population (Cohort A and B) analysis of each period was planned and performed for this endpoint.

End point type	Secondary

End point timeframe:

Factor/BPA prophylaxis period: from Day -168 to Day -1; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Efficacy Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	65		
Units: episodes per subject per year				
number (confidence interval 95%)	5.002 (3.424 to 7.305)	2.222 (1.190 to 4.152)		

Statistical analyses

Statistical analysis title	Factor/BPA Prophylaxis vs Fitusiran 80 mg Efficacy

Statistical analysis description:

Number of subjects included in this analysis was 65 and not 130.

Comparison groups	Overall Factor/BPA Prophylaxis Period v Overall Fitusiran 80 mg Efficacy Period
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	ABR ratio
Point estimate	0.444
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.234
upper limit	0.842

Secondary: Observed Annualised Spontaneous Bleeding Rate

End point title	Observed Annualised Spontaneous Bleeding Rate

End point description:

BE: any occurrence of hemorrhage that might require administration of factor/BPA. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered part of original BE and was counted as 1 BE towards ABR. Bleeding began after 72 hours from last injection at that location was considered as a new event. Spontaneous BE: bleeding event occurred for no apparent or known reason, particularly into joints, muscles and soft tissues. ABR = total number of qualifying BE/number of days in respective period *365.25. Analysis was performed on EAS 1 population. Data collection and combined population (Cohort A and B) analysis of each period was planned and performed for this endpoint.

End point type	Secondary

End point timeframe:

Factor/BPA prophylaxis period: from Day -168 to Day -1; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Efficacy Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	65		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	5.09 (± 7.93)	2.51 (± 7.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Joint Bleeding Rate

End point title	Estimated Annualised Joint Bleeding Rate

End point description:

BE: any hemorrhage that required administration of factor/BPA. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection to treat BE at that location was considered part of original BE; counted as 1 BE towards ABR. Bleeding after 72 hours from last injection at that location was considered as a new event. Joint BE: characterised by unusual sensation in joint ("aura") + increasing swelling/warmth over joint skin, increasing pain/progressive loss of range of motion/difficulty in limb use compared to Baseline. ABR = total number of qualifying BE/number of days in respective period *365.25. Estimated data were derived by using repeated measures NB regression model. Analysis was performed on EAS 1 population. Data collection and analysis of combined population (Cohort A and B) for each period was planned and performed for this endpoint.

End point type	Secondary

End point timeframe:

Factor/BPA prophylaxis period: from Day -168 to Day -1; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Efficacy Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	65		
Units: episodes per subject per year				
number (confidence interval 95%)	5.282 (3.647 to 7.651)	2.564 (1.440 to 4.566)		

Statistical analyses

Statistical analysis title	Factor/BPA Prophylaxis vs Fitusiran 80 mg Efficacy

Statistical analysis description:

Number of subjects included in this analysis was 65 and not 130.

Comparison groups	Overall Fitusiran 80 mg Efficacy Period v Overall Factor/BPA Prophylaxis Period
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	ABR ratio
Point estimate	0.485
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.259
upper limit	0.91

Secondary: Observed Annualised Joint Bleeding Rate

End point title	Observed Annualised Joint Bleeding Rate

End point description:

BE: any occurrence of hemorrhage that might require administration of factor/BPA. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered part of original BE and counted as 1 BE towards ABR. Bleeding began after 72 hours from last injection at that location was considered as a new event. Joint BE: characterised by unusual sensation in joint (aura) increasing swelling/warmth over joint skin, increasing pain or progressive loss of range of motion/difficulty in limb use compared to Baseline. ABR = total number of joint BE/number of days in respective period*365.25. Analysis was performed on EAS 1 population. Data collection and analysis of combined population (Cohort A and B) for each period was planned and performed for this endpoint.

End point type	Secondary

End point timeframe:

Factor/BPA prophylaxis period: from Day -168 to Day -1; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Efficacy Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	65		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	5.35 (± 8.19)	2.82 (± 7.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) Physical Health Score in the Fitusiran Treatment Period and the Factor or BPA Prophylaxis Period

End point title	Change in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) Physical Health Score in the Fitusiran Treatment Period and the Factor or BPA Prophylaxis Period

End point description:

Haem-A-QoL: subject-reported questionnaire for adults aged >=17 years with hemophilia and consisted of 46 items comprising 10 domains. Physical health domain (PHD) with 5 items were rated along 5 response options: never, rarely, sometimes, often or all the time. Raw score for PHD were transformed to scale ranged from 0 to 100, where lower scores = better physical health. Analysis was performed on EAS 1 population. Number of subjects analysed = subjects evaluable for endpoint. Least square (LS) mean & 95% confidence interval by mixed model for repeated measure (MMRM) analysis with robust sandwich covariance matrix: change from Baseline in each study period (change from Month -6 to Day 1 and change from Month -6 to Month 7) as response variable; period (factor/BPA prophylaxis & fitusiran treatment) & Baseline score (Month -6) as fixed effects. Data collection and analysis of combined population (Cohort A & B) for each period was planned and performed for this endpoint.

End point type	Secondary

End point timeframe:

Month -6 of prophylaxis period (Baseline), Day 1 (Month 1) and Month 7 of fitusiran treatment period

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Treatment Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: score on a scale				
least squares mean (confidence interval 95%)	-6.00 (-10.19 to -1.81)	-9.60 (-15.35 to -3.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemophilia A Quality of Life Questionnaire for Adults Total Score in the Fitusiran Treatment Period and the Factor or BPA Prophylaxis Period

End point title	Change in Haemophilia A Quality of Life Questionnaire for Adults Total Score in the Fitusiran Treatment Period and the Factor or BPA Prophylaxis Period

End point description:

Haem-A-QoL: questionnaire for adults aged >= 17 years with hemophilia; and consisted 46 items comprising 10 domains: physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality. Items were rated on 5 response options: never, rarely, sometimes, often or all time. Each domain raw score was transformed to scale ranged from 0 to 100, where lower scores=better health. Haem-A-QoL Total Score: average of all domain scores, ranged from 0 to 100; lower scores=better quality of life. EAS1. Number of subjects analysed=subjects evaluable. LS mean & 95% confidence interval by MMRM analysis with robust sandwich covariance matrix: change from Baseline in each period (change from Month -6 to Day 1 and to Month 7) as response variable; period (factor/BPA prophylaxis & fitusiran treatment) & Baseline score (Month -6) as fixed effects. Data collection and combined analysis (Cohort A&B) performed.

End point type	Secondary

End point timeframe:

Month -6 of prophylaxis period (Baseline), Day 1 (Month 1) and Month 7 of fitusiran treatment period

End point values	Overall Factor/BPA Prophylaxis Period	Overall Fitusiran 80 mg Treatment Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: score on a scale				
least squares mean (confidence interval 95%)	-3.07 (-5.56 to -0.58)	-7.62 (-10.26 to -4.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Bleeding Rate in the Fitusiran Onset Period

End point title	Estimated Annualised Bleeding Rate in the Fitusiran Onset Period

End point description:

BE: any occurrence of hemorrhage that might require administration of factor/BPA. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered part of original BE and was counted as 1 BE towards ABR. Bleeding began after 72 hours from last injection at that location was considered as new event. Estimated ABR and 95% CI was derived by using repeated measures NB regression model with logarithm of duration (years) that each subject spends in 1-Month fitusiran onset period matching BE data being analysed as offset variable. ABR = total number of qualifying BE/number of days in respective period *365.25. EAS 1 population. Number of subjects analysed=subjects evaluable. Overall analysis was performed for Fitusiran 80 mg 1-month onset period and reported in this endpoint. Data collection & combined analysis (Cohort A and B) was planned and performed.

End point type	Secondary

End point timeframe:

Day 1 up to Day 28 or up to the last day of bleeding follow up (any day up to Day 28)

End point values	Overall Fitusiran 80 mg 1-Month Onset Period			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: episodes per subject per year				
number (confidence interval 95%)	5.419 (3.716 to 7.901)			

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Annualised Bleeding Rate in the Fitusiran Onset Period

End point title	Observed Annualised Bleeding Rate in the Fitusiran Onset Period

End point description:

BE: any occurrence of hemorrhage that might require administration of factor/BPA. BE start time: time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered a part of original BE and was counted as one BE towards ABR. Bleeding began after 72 hours from last injection at that location was considered as a new event. ABR= total number of qualifying BE/number of days in the 1-month onset

period *365.25. Analysis was based on on-treatment strategy which included all treated bleeding events in 1-month onset period and excluded any bleeding events in period of intercurrent events. Analysis was performed on EAS 1 population. Data collection and combined analysis (Cohort A and B) for 1-Month onset period was planned and performed.

End point type	Secondary

End point timeframe:

Day 1 up to Day 28 or up to the last day of bleeding follow up (any day up to Day 28)

End point values	Overall Fitusiran 80 mg 1-Month Onset Period			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: episodes per subject per year				
arithmetic mean (standard deviation)	5.42 (± 8.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Bleeding Rate in the Fitusiran Treatment Period

End point title	Estimated Annualised Bleeding Rate in the Fitusiran Treatment Period

End point description:

BE: defined as any occurrence of hemorrhage that might require administration of factor/BPA. BE start time was time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered a part of original BE and counted as one BE towards ABR. Bleeding began after 72 hours from last injection at that location was considered as new event. Analysis was based on on-treatment strategy which included all treated bleeding events in fitusiran period and excluded any bleeding events in the period of intercurrent events. ABR = total number of qualifying BE/number of days in respective period *365.25. Analysis was performed on EAS 1 population. Data collection and analysis of combined population (Cohort A and B) for treatment period was planned and performed.

End point type	Secondary

End point timeframe:

from Day 1 up to Day 190

End point values	Overall Fitusiran 80 mg Treatment Period			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: episodes per subject per year				
number (confidence interval 95%)	3.317 (2.111 to 5.211)			

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Annualised Bleeding Rate in the Fitusiran Treatment Period

End point title	Observed Annualised Bleeding Rate in the Fitusiran Treatment Period

End point description:

BE: any occurrence of hemorrhage that might require administration of factor/BPA. BE start time was time at which 1st BE symptoms develop; bleeding/any symptoms at same location that occurred within 72 hours of last injection used to treat BE at that location was considered a part of original bleeding event and was counted as one BE towards ABR. Any bleeding that began after 72 hours from last injection at that location was considered as a new event. ABR= total number of qualifying BE/number of days in treatment period *365.25. Analysis was based on on-treatment strategy which included all treated bleeding events in fitusiran period and excluded any bleeding events in period of intercurrent events. Analysis was performed on EAS1 population. Data collection and analysis of combined population (Cohort A and B) for treatment period was planned and performed.

End point type	Secondary

End point timeframe:

from Day 1 up to Day 190)

End point values	Overall Fitusiran 80 mg Treatment Period			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: episodes per subject per year				
arithmetic mean (standard deviation)	3.48 (± 6.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A: Annualised Weight-adjusted Consumption of BPA (Activated Prothrombin Complex Concentrates)

End point title	Cohort A: Annualised Weight-adjusted Consumption of BPA (Activated Prothrombin Complex Concentrates)

End point description:

Annualised weight-adjusted BPA consumption was calculated for each subject during prophylaxis period as: [Sum of BPA dose per body weight received during corresponding period/number of days in corresponding period]*365.25. In this endpoint, data of annualised weight-adjusted consumption of BPA agent: aPCC (unit per kilogram [U/kg]) were reported. Combined data of annualised weight-adjusted BPA consumption (U/kg) for both treated bleeds and prophylaxis purpose were reported in this endpoint. Analysis was performed on EAS 1 population. Here, 'number of subjects analysed' = subjects evaluable

for this endpoint.

End point type	Secondary

End point timeframe:

From Day -168 to Day -1 of BPA prophylaxis period; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	BPA Prophylaxis: Cohort: A Inhibitor	Fitusiran 80 mg Prophylaxis: Cohort A: Inhibitor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: U/kg per subject per year				
arithmetic mean (standard deviation)	7912.7 (± 5507.6)	39.7 (± 87.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A: Annualised Weight-adjusted Consumption of BPA (Recombinant Factor VIIa)

End point title	Cohort A: Annualised Weight-adjusted Consumption of BPA (Recombinant Factor VIIa)

End point description:

Annualised weight-adjusted BPA consumption was calculated for each subject during prophylaxis period as: [Sum of BPA dose per body weight received during corresponding period/number of days in corresponding period]*365.25. In this endpoint, data of annualised weight-adjusted consumption of BPA agents: rFVIIa (unit: micrograms per kg [mcg/kg]) were reported. Combined data of annualised weight-adjusted BPA consumption (mcg/kg) for both treated bleeds and prophylaxis purpose were reported in this endpoint. Analysis was performed on EAS 1 population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Day -168 to Day -1 of BPA prophylaxis period; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	BPA Prophylaxis: Cohort: A Inhibitor	Fitusiran 80 mg Prophylaxis: Cohort A: Inhibitor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: mcg/kg per subject per year				
arithmetic mean (standard deviation)	18895.8 (± 14081.9)	168.8 (± 290.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort B: Annualised Weight-adjusted Consumption of Factor

End point title	Cohort B: Annualised Weight-adjusted Consumption of Factor

End point description:

Annualised weight-adjusted BPA consumption was calculated for each subject during prophylaxis period as: [Sum of BPA dose per body weight received during corresponding period/number of days in corresponding period]*365.25. In this endpoint, data of annualised weight-adjusted consumption of BPA agents: FVIII and FIX (unit: international Units [IU] per kg [IU/kg]) were reported. Combined data of annualised weight-adjusted BPA consumption (IU/kg) for both treated bleeds and prophylaxis purpose were reported in this endpoint. Analysis was performed on EAS 1 population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

From Day -168 to Day -1 of factor prophylaxis period; 6-month fitusiran efficacy period: from Day 29 to Day 190 or up to the last day of bleeding follow up (any day up to Day 190), whichever was the earliest

End point values	Factor Prophylaxis: Cohort B: Non-inhibitor	Fitusiran 80 mg Prophylaxis: Cohort B: Non-inhibitor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: IU/kg per subject per year				
arithmetic mean (standard deviation)				
FVIII (n = 36, 36)	3396.9 (± 1144.5)	60.7 (± 148.3)		
FIX (n = 10, 10)	3175.5 (± 961.3)	17.8 (± 56.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Factor/BPA prophylaxis period: from Day -168 to Day -1; Fitusiran 80 mg QM/50 mg Q2M period: from Day 1 of fitusiran treatment period (i.e., 1 month onset+ 6 months efficacy) until antithrombin (AT) follow up (i.e. up to 21 months)

Adverse event reporting additional description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject who received study drug which did not necessarily have a causal relationship with the treatment. Safety analysis set (SAS): all subjects who were enrolled and received any dose of fitusiran (80 mg, QM before dose pause; SAS 1)/(50 mg, Q2M after dose pause; SAS 2).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Cohort A: SAS 1 - BPA Prophylaxis

Reporting group description:

Subjects with hemophilia A or B, with inhibitory antibodies to FVIII or FIX and who were receiving BPA prophylaxis were enrolled in the study and entered the 6-month BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with BPAs.

Reporting group title	Cohort A: SAS 1 - Fitusiran 80 mg QM

Reporting group description:

Post completion of BPA prophylaxis period, subjects entered into the 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period) and received fitusiran 80 mg until sponsor initiated a voluntary dose pause. Subjects could continue to receive BPA prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. A subgroup of Cohort A (hemophilia B subjects with inhibitory antibodies to Factor IX who were not responding adequately to BPA prophylaxis treatment: historical ABR >=20) entered directly into fitusiran treatment period. Throughout the study, subjects in the fitusiran treatment period received could on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate. Post last fitusiran dose, subjects had a safety follow-up/AT activity level follow-up up to 6 months (monthly monitor until AT activity levels return to approximately 60% or per Investigator discretion).

Reporting group title	Cohort B: SAS 1 - Factor Prophylaxis

Reporting group description:

Subjects with hemophilia A or B, without inhibitory antibodies to FVIII or FIX and who were receiving factor prophylaxis were enrolled in the study and entered the 6-month BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with factor concentrates.

Reporting group title	Cohort B: SAS 1 - Fitusiran 80 mg QM

Reporting group description:

Post completion of Factor prophylaxis period, subjects entered into the 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period) and received fitusiran 80 mg until sponsor initiated a voluntary dose pause. Subjects could continue to receive BPA prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. Throughout the study, subjects in the fitusiran treatment period received could on-demand treatment for breakthrough bleeding episodes with factor, as appropriate. Post last fitusiran dose, subjects had a safety follow-up/AT activity level follow-up up to 6 months (monthly monitor until AT activity levels return to approximately 60% or per Investigator discretion).

Reporting group title	Overall: SAS 1 - Factor/BPA Prophylaxis

Reporting group description:

All subjects whether with inhibitory antibodies (Cohort A) or without inhibitory antibodies (Cohort B) to FVIII or FIX and who were receiving BPA or factor prophylaxis, respectively, were enrolled in the study and entered the 6-month factor or BPA prophylaxis period in this study and continued their pre-study regularly scheduled prophylaxis regimen with BPAs or factors in 6-month factor or BPA prophylaxis period. This period was skipped by a subgroup of Cohort A which included subjects with hemophilia B with inhibitory antibodies to FIX and who had not respond adequately to BPA prophylaxis prior to study entry (historical ABR >=20).

Reporting group title	Overall: SAS 1 - Fitusiran 80 mg QM

Reporting group description:

Post completion of BPA prophylaxis period, all subjects who received fitusiran 80 mg QM (either in Cohort A or Cohort B) until sponsor initiated a voluntary dose pause. Subjects could continue to receive BPA/factor prophylaxis for up to 7 days after start of fitusiran treatment on Day 1. A subgroup of Cohort A (hemophilia B subjects with inhibitory antibodies to Factor IX who were not responding adequately to BPA prophylaxis treatment: historical ABR >=20) entered directly into fitusiran treatment period. Throughout the study, subjects in the fitusiran treatment period received could on-demand treatment for breakthrough bleeding episodes with BPAs or factors, as appropriate. Post last fitusiran dose, subjects had a safety follow-up/AT activity level follow-up up to 6 months (monthly monitor until AT activity levels return to approximately 60% or per Investigator discretion).

Reporting group title	Cohort A: SAS 2 - BPA Prophylaxis

Reporting group description:

Subjects with hemophilia A or B, with inhibitory antibodies to FVIII or FIX and who were receiving BPA prophylaxis were enrolled in the study and entered the 6-month BPA prophylaxis period in this study and continued their pre-study, regularly scheduled prophylaxis regimen with BPAs.

Reporting group title	Cohort A: SAS 2 - Fitusiran 50 mg Q2M

Reporting group description:

Post completion of BPA prophylaxis period, subjects entered into the 7-month fitusiran treatment period (1-month onset period + 6-month efficacy period) and received fitusiran 50 mg Q2M after sponsor initiated a voluntary dose pause. Throughout the study, subjects in the fitusiran treatment period received could on-demand treatment for breakthrough bleeding episodes with BPAs, as appropriate. Post last fitusiran dose, subjects had a safety follow-up/AT activity level follow-up up to 6 months (monthly monitor until AT activity levels return to approximately 60% or per Investigator discretion).

Serious adverse events	Cohort A: SAS 1 - BPA Prophylaxis	Cohort A: SAS 1 - Fitusiran 80 mg QM	Cohort B: SAS 1 - Factor Prophylaxis
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)	5 / 21 (23.81%)	0 / 46 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
C-Reactive Protein Increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Biliary Neoplasm			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur Fracture			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Central Venous Catheter Removal			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis Acute			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma Late Onset			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Stevens-Johnson Syndrome			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Haemarthrosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilic Arthropathy			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Covid-19 Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Device Infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort B: SAS 1 - Fitusiran 80 mg QM	Overall: SAS 1 - Factor/BPA Prophylaxis	Overall: SAS 1 - Fitusiran 80 mg QM
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 46 (8.70%)	5 / 65 (7.69%)	9 / 67 (13.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
C-Reactive Protein Increased			

subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Biliary Neoplasm			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Central Venous Catheter Removal			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis Acute			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Asthma Late Onset			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Stevens-Johnson Syndrome			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilic Arthropathy			
subjects affected / exposed	1 / 46 (2.17%)	2 / 65 (3.08%)	2 / 67 (2.99%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Covid-19 Pneumonia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Device Infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort A: SAS 2 - BPA Prophylaxis	Cohort A: SAS 2 - Fitusiran 50 mg Q2M	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	1 / 2 (50.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
C-Reactive Protein Increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Biliary Neoplasm			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central Venous Catheter Removal			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis Acute			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma Late Onset			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Stevens-Johnson Syndrome			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilic Arthropathy			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19 Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort A: SAS 1 - BPA Prophylaxis	Cohort A: SAS 1 - Fitusiran 80 mg QM	Cohort B: SAS 1 - Factor Prophylaxis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 19 (52.63%)	13 / 21 (61.90%)	9 / 46 (19.57%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 19 (5.26%)	3 / 21 (14.29%)	0 / 46 (0.00%)
occurrences (all)	3	3	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences (all)	1	3	0
Fibrin D Dimer Increased			

subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Lymphocyte Count Increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Neutrophil Count Decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences (all)	1	1	0
Buttock Injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	1 / 46 (2.17%)
occurrences (all)	2	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Injection Site Pain			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 46 (0.00%)
occurrences (all)	0	2	0

Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Dental Caries			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	1 / 46 (2.17%)
occurrences (all)	2	0	1
Eosinophilic Oesophagitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Motility Disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Teething			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 46 (0.00%)
occurrences (all)	0	2	0

Cholelithiasis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Hepatic Steatosis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	1 / 46 (2.17%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	3 / 46 (6.52%)
occurrences (all)	1	1	4
Joint Swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Synovitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 46 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Genital Herpes Simplex			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	2 / 46 (4.35%)
occurrences (all)	1	1	2
Nasopharyngitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Tinea Pedis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	1 / 46 (2.17%)
occurrences (all)	1	0	1

Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 19 (15.79%)	4 / 21 (19.05%)	1 / 46 (2.17%)
occurrences (all)	4	5	1
Metabolism and nutrition disorders			
Iron Deficiency			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort B: SAS 1 - Fitusiran 80 mg QM	Overall: SAS 1 - Factor/BPA Prophylaxis	Overall: SAS 1 - Fitusiran 80 mg QM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 46 (60.87%)	19 / 65 (29.23%)	41 / 67 (61.19%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	15 / 46 (32.61%)	1 / 65 (1.54%)	18 / 67 (26.87%)
occurrences (all)	19	3	22
Aspartate Aminotransferase Increased			
subjects affected / exposed	3 / 46 (6.52%)	1 / 65 (1.54%)	4 / 67 (5.97%)
occurrences (all)	4	1	7
Fibrin D Dimer Increased			
subjects affected / exposed	2 / 46 (4.35%)	0 / 65 (0.00%)	5 / 67 (7.46%)
occurrences (all)	2	0	5
Lymphocyte Count Increased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	0 / 67 (0.00%)
occurrences (all)	0	0	0
Neutrophil Count Decreased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	0 / 67 (0.00%)
occurrences (all)	0	0	0
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	0 / 67 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	1 / 67 (1.49%)
occurrences (all)	0	1	1
Buttock Injury			

subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 46 (0.00%)	2 / 65 (3.08%)	0 / 67 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 46 (0.00%)	3 / 65 (4.62%)	1 / 67 (1.49%)
occurrences (all)	0	3	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 46 (0.00%)	2 / 65 (3.08%)	0 / 67 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	3 / 67 (4.48%)
occurrences (all)	2	0	4
Injection Site Pain			
subjects affected / exposed	3 / 46 (6.52%)	0 / 65 (0.00%)	5 / 67 (7.46%)
occurrences (all)	3	0	5
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	3 / 67 (4.48%)
occurrences (all)	1	0	4
Dental Caries			
subjects affected / exposed	0 / 46 (0.00%)	2 / 65 (3.08%)	0 / 67 (0.00%)
occurrences (all)	0	3	0
Eosinophilic Oesophagitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal Motility Disorder			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 46 (0.00%)	0 / 65 (0.00%)	0 / 67 (0.00%)
occurrences (all)	0	0	0

Nausea			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Teething			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	1 / 46 (2.17%)	0 / 65 (0.00%)	2 / 67 (2.99%)
occurrences (all)	1	0	2
Vomiting			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	1 / 67 (1.49%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 46 (4.35%)	0 / 65 (0.00%)	4 / 67 (5.97%)
occurrences (all)	2	0	5
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 46 (4.35%)	0 / 65 (0.00%)	4 / 67 (5.97%)
occurrences (all)	2	0	4
Cholelithiasis			
subjects affected / exposed	3 / 46 (6.52%)	0 / 65 (0.00%)	5 / 67 (7.46%)
occurrences (all)	3	0	5
Hepatic Steatosis			
subjects affected / exposed	1 / 46 (2.17%)	1 / 65 (1.54%)	3 / 67 (4.48%)
occurrences (all)	1	1	3
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	4 / 46 (8.70%)	4 / 65 (6.15%)	5 / 67 (7.46%)
occurrences (all)	8	5	9
Joint Swelling			
subjects affected / exposed	1 / 46 (2.17%)	1 / 65 (1.54%)	1 / 67 (1.49%)
occurrences (all)	1	1	1
Synovitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	1 / 67 (1.49%)
occurrences (all)	0	1	1
Infections and infestations			
Genital Herpes Simplex			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 46 (2.17%)	3 / 65 (4.62%)	2 / 67 (2.99%)
occurrences (all)	1	3	2
Nasopharyngitis			
subjects affected / exposed	7 / 46 (15.22%)	1 / 65 (1.54%)	8 / 67 (11.94%)
occurrences (all)	9	1	10
Tinea Pedis			
subjects affected / exposed	0 / 46 (0.00%)	2 / 65 (3.08%)	0 / 67 (0.00%)
occurrences (all)	0	2	0
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 46 (4.35%)	4 / 65 (6.15%)	6 / 67 (8.96%)
occurrences (all)	2	5	7
Metabolism and nutrition disorders			
Iron Deficiency			
subjects affected / exposed	0 / 46 (0.00%)	1 / 65 (1.54%)	0 / 67 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort A: SAS 2 - BPA Prophylaxis	Cohort A: SAS 2 - Fitusiran 50 mg Q2M	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	2 / 2 (100.00%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Aspartate Aminotransferase			

Increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Fibrin D Dimer Increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Lymphocyte Count Increased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Neutrophil Count Decreased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Buttock Injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Injection Site Erythema			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Injection Site Pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dental Caries			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Eosinophilic Oesophagitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal Motility Disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Teething			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Toothache			
subjects affected / exposed	0 / 2 (0.00%)	2 / 2 (100.00%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cholelithiasis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hepatic Steatosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Joint Swelling			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Synovitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Genital Herpes Simplex			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Influenza			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tinea Pedis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Iron Deficiency			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2017	The following changes were done: • One death was reported in a subject with cerebral venous sinus thrombosis (CVST) in another fitusiran study, which was considered possibly related to fitusiran. Accordingly, the primary purpose of this protocol amendment was to implement additional safety measures to mitigate the risk of thrombosis in the lowered-AT setting induced by fitusiran therapy in the context of concomitant use of BPAs (bypassing agents) for bleed management. This included updating the bleed management guidelines, outlining recommendations for the monitoring and management of thrombotic events, clarification on the definitions for bleeding episodes, revising the recommendations for the management of sepsis, and adding additional exploratory laboratory assessments. • Changed the population studied, i.e., the population was only consisted of subjects who had an inhibitory antibody to FVIII or FIX, whereas previously the study design included both subjects with and without inhibitory antibodies to FVIII or FIX; as such, given the known prevalence, the planned sample size had been reduced to N=30. • A list of the primary changes implemented was provided in protocol. Corrections communicated in a previous administrative change letter were applied.
31 May 2018	The following changes were done: • Clinical development and commercialisation of fitusiran were granted from Alnylam Pharmaceuticals, Inc. to Genzyme Corporation, a Sanofi Company, which assumed responsibility of the current clinical program. Therefore, the Alnylam logo and reference to Alnylam was changed to “the Sponsor” or “Sanofi Genzyme” as appropriate throughout the protocol. The Sanofi Genzyme study code (EFC15110) was added, and the Alnylam study drug code ALN-AT3SC was also updated to the generic drug name fitusiran. Several sections were created or updated to reflect the Sanofi Genzyme environment. • Expanded to include non-inhibitor subjects under prophylaxis with factor concentrates while inhibitor subjects had higher unmet needs compared to non-inhibitor subjects, there was no known difference in risks between these 2 populations based on the mechanism of action of fitusiran or factor/BPA therapy.
18 December 2018	The following changes was done: • Extended worldwide the inclusion of a subgroup of Cohort A subjects with hemophilia B (with inhibitory antibodies to Factor IX, who were not responding adequately to BPA prophylaxis (treatment defined as ABR >=20) to start treatment with fitusiran directly after the screening period, limiting however the inclusion to up to 4 subjects. A secondary objective and endpoint were included to further assess fitusiran efficacy.
25 November 2020	The following changes were done: • Introduction of a risk mitigation strategy for vascular thrombotic events in subjects exposed to fitusiran. To decrease AT lowering with fitusiran dosing regimen was changed from 80 mg QM to 50 mg Q2M. A Schedule of Assessments was added to accommodate the new AT-driven dose regimen and to ensure optimal monitoring during the transition. • Study expanded to include 80 subjects to mitigate for the over enrollment of the non-inhibitor cohort as there were already 79 subjects enrolled at the time of this amendment (i.e., approximately n=30 for Cohort A and approximately n=50 for Cohort B). • Cholecystitis and cholelithiasis had been added to the protocol as adverse events of special interest (AESIs). • 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 COVID-19 pandemic.

08 December 2020	The following changes were done - • To minimise the time between two AT measurements if the first AT result was <15%. "Upon the first AT level <15%, the subject must have another AT activity level sample drawn within 1 week of site receipt of the results. If this result is <15%, this will be considered the second AT activity level <15%" had been added to mandate a second AT activity level within 1 week of site receipt of an initial AT level result <15%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 October 2020	A dosing pause period for the original dose regimen (80 mg QM) was implemented on due to thrombotic events observed within the fitusiran clinical study program.	-

Notes:

Limitations and caveats

None reported