Clinical trial results:
ATLAS-INH: A Phase 3 study to evaluate the efficacy and safety of fitusiran in patients with hemophilia A or B, with inhibitory antibodies to factor VIII or IX

Summary

EudraCT number	2016-001463-36
Trial protocol	GB BG HU ES PT FR DE DK NL IT Outside EU/EEA
Global end of trial date	23 June 2021

Results information

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

Trial information

Trial identification

Sponsor protocol code	EFC14768

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03417102
WHO universal trial number (UTN)	U1111-1251-5163
Other trial identifiers	Alnylam: ALN-AT3SC-003

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
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	19 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adults and adolescents subjects. The parent(s) or guardian(s) as well as the children 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 child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may 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:

Long term follow-up: The follow-up period lasted from 1 to 6 months (as follow-up for subjects in the fitusiran treatment arm who did not enroll in the extension study (LTE15174 [NCT03754790]), due to the requirement for the antithrombin (AT) activity level to return to approximately 60% following the final dose). In lieu of the long term follow-up period, subjects who completed the study were eligible to enroll in an open-label extension study (LTE15174).

Evidence for comparator: -

Actual start date of recruitment	14 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	India: 20
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Australia: 2

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Turkey: 6
Worldwide total number of subjects	57
EEA total number of subjects	1

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)	10
Adults (18-64 years)	47
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 58 centres in 17 countries. A total of 85 subjects were screened between 14 February 2018 to 19-Mar-2021, of which 25 subjects were screen failure. Screen failures were mainly due to the presence of clinically significant liver disease. A total of 60 subjects were enrolled in the study.

Pre-assignment

Screening details:

57 subjects randomised in 2:1 ratio to fitusiran prophylaxis and on-demand arms; stratified by number of bleeding episodes prior to Screening (<=10 vs >10). 3 subjects from China were treated with fitusiran but not randomised. These subjects were considered in fitusiran prophylaxis arm for safety analysis, but not in any other analysis.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bypassing agents (BPA) on-demand

Arm description:

Subjects received On-demand BPAs (use of these agents, as needed, for episodic bleeding episodes, and not on a regular regimen intended to prevent spontaneous bleeding) per Investigator discretion from Day 1 for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Arm type	Active comparator
Investigational medicinal product name	Bypassing agents (BPA) on-demand
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Per Investigator discretion from Day 1 for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Arm title	Fitusiran 80 mg Prophylaxis

Arm description:

Subjects received fitusiran 80 mg subcutaneously (SC) as prophylaxis once monthly from Day 1, along with the on-demand BPAs (per investigator's discretion and within bleeding dosing guidelines) for treatment of breakthrough bleeding episodes, up to a total of 9 months.

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 SC injection once monthly, on Day 1 of the treatment period for a total of 9 months.

Number of subjects in period 1	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis
Started	19	38
Completed	19	33
Not completed	0	5
Adverse event, non-fatal	-	1
Related to Coronavirus Pandemic (Covid-19)	-	3
Unspecified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Bypassing agents (BPA) on-demand
Reporting group description:	
Subjects received On-demand BPAs (use of these agents, as needed, for episodic bleeding episodes, and not on a regular regimen intended to prevent spontaneous bleeding) per Investigator discretion from Day 1 for treatment of breakthrough bleeding episodes, up to a total of 9 months.	
Reporting group title	Fitusiran 80 mg Prophylaxis
Reporting group description:	
Subjects received fitusiran 80 mg subcutaneously (SC) as prophylaxis once monthly from Day 1, along with the on-demand BPAs (per investigator's discretion and within bleeding dosing guidelines) for treatment of breakthrough bleeding episodes, up to a total of 9 months.	

Reporting group values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis	Total
Number of subjects	19	38	57
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	31.5	26.8	
standard deviation	± 13.1	± 9.8	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	19	38	57
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	13	26	39
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	6	10	16
Other	0	1	1
Multiple	0	1	1
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Bypassing agents (BPA) on-demand

Reporting group description:

Subjects received On-demand BPAs (use of these agents, as needed, for episodic bleeding episodes, and not on a regular regimen intended to prevent spontaneous bleeding) per Investigator discretion from Day 1 for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Reporting group title	Fitusiran 80 mg Prophylaxis

Reporting group description:

Subjects received fitusiran 80 mg subcutaneously (SC) as prophylaxis once monthly from Day 1, along with the on-demand BPAs (per investigator's discretion and within bleeding dosing guidelines) for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Subject analysis set title	BPA on-demand
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received On-demand BPAs (use of these agents, as needed, for episodic bleeding episodes, and not on a regular regimen intended to prevent spontaneous bleeding) per Investigator discretion from Day 1 for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Subject analysis set title	Fitusiran Prophylaxis
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received fitusiran 80 mg subcutaneously (SC) as prophylaxis once monthly from Day 1, along with the on-demand BPAs (per investigator's discretion and within bleeding dosing guidelines) for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Primary: Estimated Annualised Bleeding Rate (ABR) for Treated Bleeds During the Efficacy Period

End point title	Estimated Annualised Bleeding Rate (ABR) for Treated Bleeds During the Efficacy Period

End point description:

ABR for subject during efficacy period (EP) was defined as annualised number of bleeding episodes during EP annualised to a 1-year interval of time. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BPA or factor. It started from first sign of a bleed and ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location or injections less than or equal to (<=) 72 hours apart were considered the same bleeding episode. EP was defined as time duration starting from Day 29 when antithrombin (AT) lowering capacity of fitusiran had achieved therapeutic target range to the earliest of (Day 246 or last day of bleeding follow up)(maximum duration of EP: from Day 29 to Day 246). This endpoint represents estimated results (i.e., results received by applying negative binomial [NB] regression model on data collected during EP). Analysis was performed on ITT population which included all randomised subjects.

End point type	Primary

End point timeframe:

From Day 29 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
number (confidence interval 95%)	18.071 (10.598 to	1.666 (1.014 to 2.736)		

30.812)

Statistical analyses

Statistical analysis title	Fitusiran rate versus BPA on-demand rate
Comparison groups	Bypassing agents (BPA) on-demand v Fitusiran 80 mg Prophylaxis
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Negative binomial regression model
Parameter estimate	ABR ratio
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.192

Notes:

[1] - P-value derived from NB regression model, accounted for different follow-up times during EP, with treatment arm and randomisation strata of number of bleeds in 6 months prior to study (<=10,>10) as fixed effects. Significance threshold was 0.05.

Primary: Observed Annualised Bleeding Rate (ABR) for Treated Bleeds During the Efficacy Period

End point title	Observed Annualised Bleeding Rate (ABR) for Treated Bleeds During the Efficacy Period[2]

End point description:

ABR for subject during EP was defined as annualised number of bleeding episodes during EP annualised to a 1-year interval of time. ABR= number of bleeding episodes during EP divided by total number of days during EP*365.25. A bleeding episode was defined as any occurrence of hemorrhage that required administration of BPA or factor. It started from the first sign of a bleed and ended no more than 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections <=72 hours apart were considered the same bleeding episode. EP was defined as time duration starting from Day 29 when the AT lowering capacity of fitusiran had achieved therapeutic target range to the earliest of (Day 246 or the last day of bleeding follow up) (maximum duration of EP: from Day 29-Day 246). This endpoint represents observed results (i.e., descriptive statistics values based on the data which was collected during EP). Analysis was performed on ITT population.

End point type	Primary

End point timeframe:

From Day 29 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), 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 performed.

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	18.1 (± 14.9)	1.7 (± 3.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Bleeding Rate (ABR) for Treated Bleeds During the Treatment Period

End point title	Estimated Annualised Bleeding Rate (ABR) for Treated Bleeds During the Treatment Period

End point description:

ABR for subject during treatment period (TP) was defined as annualised number of bleeding episodes during TP annualised to a 1-year interval of time. Bleeding episode: any occurrence of hemorrhage that required administration of BPA or factor. It started from first sign of a bleed and ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location or injections <= 72 hours apart were considered the same bleeding episode. TP was sum of onset period (first 28 days after first dose of fitusiran) and EP (starting on Day 29 when AT lowering capacity of fitusiran had achieved therapeutic target range to earliest of [Day 246 or last day of bleeding follow up])(maximum duration of TP: from Day 1 to Day 246). This endpoint represents estimated results (i.e., results received by applying NB regression model on data collected during TP). Analysis was performed on intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

From Day 1 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
number (confidence interval 95%)	18.819 (11.541 to 30.687)	2.024 (1.306 to 3.138)		

Statistical analyses

Statistical analysis title	Fitusiran rate versus BPA on-demand rate
Comparison groups	Bypassing agents (BPA) on-demand v Fitusiran 80 mg Prophylaxis

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Negative binomial regression model
Parameter estimate	ABR ratio
Point estimate	0.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.056
upper limit	0.207

Notes:

[3] - P-value derived from NB regression model, accounted for different follow-up times during TP, with treatment arm and randomisation strata of number of bleeds in 6 months prior to study (<=10,>10) as fixed effects. Significance threshold was 0.05.

Secondary: Observed Annualised Bleeding Rate (ABR) for Treated Bleeds During the Treatment Period

End point title	Observed Annualised Bleeding Rate (ABR) for Treated Bleeds During the Treatment Period

End point description:

ABR for subject during TP was defined as annualised number of bleeding episodes during TP annualised to 1-year interval of time. ABR= number of bleeding episodes during TP divided by total number of days during TP*365.25. Bleeding episode: any occurrence of hemorrhage that required administration of BPA or factor. It started from first sign of bleed and ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location or injections <=72 hours apart were considered same bleeding episode. TP was sum of onset period (first 28 days after the first dose of fitusiran) and EP (starting on Day 29 when AT lowering capacity of fitusiran had achieved therapeutic target range to the earliest of [Day 246 or the last day of bleeding follow up]) (maximum duration of TP: from Day 1-Day 246). This endpoint represents observed results (i.e., descriptive statistics values based on data collected during TP). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	18.8 (± 15.4)	2.0 (± 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Spontaneous Bleeding Rate for Treated Bleeds During Efficacy Period

End point title	Estimated Annualised Spontaneous Bleeding Rate for Treated Bleeds During Efficacy Period

End point description:

Annualised spontaneous bleeding rate for subject during EP was defined as annualised number of spontaneous bleeding episodes during EP annualised to a 1-year interval of time. Spontaneous bleeding episode was bleeding event that occurred for no apparent or known reason, particularly into joints, muscles, and soft tissues. It started from first sign of a bleed and ended no more than 72 hours after last treatment for the bleed, within which any symptoms of bleeding at the same location or injections <=72 hours apart were considered the same bleeding episode. EP was defined as time duration starting from Day 29 when AT lowering capacity of fitusiran had achieved therapeutic target range to the earliest of (Day 246 or last day of bleeding follow up) (maximum duration of EP: from Day 29-Day 246). This endpoint represents estimated results (i.e., results received by applying NB regression model on data collected during EP). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 29 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
number (confidence interval 95%)	15.675 (9.281 to 26.471)	0.872 (0.491 to 1.551)		

Statistical analyses

Statistical analysis title	Fitusiran rate versus BPA on-demand rate
Comparison groups	Bypassing agents (BPA) on-demand v Fitusiran 80 mg Prophylaxis
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Negative binomial regression model
Parameter estimate	ABR ratio
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.121

Notes:

[4] - P-value derived from NB regression model, accounted for different follow-up times during EP, with treatment arm and randomisation strata of number of bleeds in 6 months prior to study (<=10,>10) as fixed effects. Significance threshold was 0.05.

Secondary: Observed Annualised Spontaneous Bleeding Rate for Treated Bleeds During the Efficacy Period

End point title	Observed Annualised Spontaneous Bleeding Rate for Treated

	Bleeds During the Efficacy Period

End point description:

ABR for subject during EP: annualised number of spontaneous bleeding episodes during EP annualised to 1-year interval of time. ABR=number of treated spontaneous bleeding episodes during EP divided by total number of days during EP*365.25. Spontaneous bleeding episode was bleeding event that occurred for no apparent or known reason, into joints, muscles, and soft tissues. It started from the first sign of a bleed and ended no more than 72 hours after the last treatment for bleed, within which any symptoms of bleeding at the same location or injections <=72 hours apart were considered the same bleeding episode. EP: time duration starting from Day 29 when AT lowering capacity of fitusiran had achieved therapeutic target range to earliest of (Day 246 or the last day of bleeding follow up)(maximum duration of EP: from Day 29-Day 246).This endpoint represents observed results (i.e., descriptive statistics values based on data collected during EP). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 29 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	15.6 (± 14.9)	0.9 (± 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Joint Bleeding Rate for Treated Bleeds During the Efficacy Period

End point title	Estimated Annualised Joint Bleeding Rate for Treated Bleeds During the Efficacy Period

End point description:

Annualised joint bleeding rate for subject during EP was defined as annualised number of bleeding episodes during EP annualised to a 1-year interval of time. Joint bleeding episode was characterised by an unusual sensation in the joint ("aura") in combination with 1) increasing swelling or warmth over the skin, joint, 2) increased pain, or 3) progressive loss of range of motion or difficulty in using the limb as compared with Baseline. It started from first sign of a bleed and ended no more than 72 hours after last treatment for the bleed. EP was defined as time duration starting from Day 29 when the AT lowering capacity of fitusiran had achieved therapeutic target range to the earliest of (Day 246 or the last day of bleeding follow up) (maximum duration of EP: from Day 29 to Day 246). This endpoint presents estimated results (i.e., results received by applying NB regression model on data collected during EP). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 29 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
number (confidence interval 95%)	13.759 (7.950 to 23.811)	1.349 (0.798 to 2.280)		

Statistical analyses

Statistical analysis title	Fitusiran rate versus BPA on-demand rate
Comparison groups	Bypassing agents (BPA) on-demand v Fitusiran 80 mg Prophylaxis
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Negative binomial regression model
Parameter estimate	ABR ratio
Point estimate	0.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.21

Notes:

[5] - P-value derived from NB regression model, accounted for different follow-up times during EP, with treatment arm and randomisation strata of number of bleeds in 6 months prior to study (<=10,>10) as fixed effects. Significance threshold was 0.05.

Secondary: Observed Annualised Joint Bleeding Rate for Treated Bleeds During the Efficacy Period

End point title	Observed Annualised Joint Bleeding Rate for Treated Bleeds During the Efficacy Period

End point description:

Annualised joint bleeding rate for subject during EP: annualised number of joint bleeding episodes during EP annualised to 1-year interval of time. ABR=number of treated joint bleeding episodes during EP divided by total number of days during EP*365.25. Joint bleeding episode was characterised by an unusual sensation in joint (“aura”) in combination with 1) increasing swelling or warmth over skin, joint, 2) increased pain, or 3) progressive loss of range of motion or difficulty in using limb as compared with Baseline. It started from first sign of bleed and ended no more than 72 hours after last treatment for bleed. EP: time duration starting from Day 29 when AT lowering capacity of fitusiran had achieved therapeutic target range to earliest of (Day 246 or last day of bleeding follow up)(maximum duration of EP: from Day 29-Day 246). Endpoint presents observed results (i.e., descriptive statistics values based on data collected during EP). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 29 up to Day 246 or up to the last day of bleeding follow up (any day up to Day 246), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	13.8 (± 12.2)	1.4 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related Quality of Life (HRQOL): Change From Baseline in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) Physical Health Domain Score at Month 9

End point title	Health-related Quality of Life (HRQOL): Change From Baseline in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) Physical Health Domain Score at Month 9

End point description:

Haem-A-QoL: subject-reported questionnaire designed for adult subjects (>=17 years of age) with hemophilia; and consisted of 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 along five response options: never, rarely, sometimes, often, or all the time. Change from baseline in physical Health domain score was reported in this endpoint. Raw score for physical health domain were transformed to a scale ranged from 0 to 100, where lower scores denoted better physical health. Analysis was performed on ITT population. Here, "number of subjects analysed" = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Month 9

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	32		
Units: score on a scale				
least squares mean (confidence interval 95%)	-1.94 (-10.32 to 6.43)	-30.67 (-36.90 to -24.43)		

Statistical analyses

Statistical analysis title	Fitusiran versus BPA on-demand
Comparison groups	Bypassing agents (BPA) on-demand v Fitusiran 80 mg Prophylaxis

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean difference
Point estimate	-28.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.07
upper limit	-18.37

Notes:

[6] - Analysis of Covariance (ANCOVA) model included treatment arm and randomisation strata of number of bleeds (<=10, > 10) as fixed effects, Baseline score as a covariate. Significance threshold was at 0.05.

Secondary: Health-related Quality of Life (HRQOL): Change From Baseline in Haem-A-QOL Total Score at Month 9

End point title	Health-related Quality of Life (HRQOL): Change From Baseline in Haem-A-QOL Total Score at Month 9

End point description:

Haem-A-QoL: subject-reported questionnaire designed for adult subjects (>=17 years of age) with hemophilia; and consisted of 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 along five response options: never, rarely, sometimes, often, or all the time. Raw score for each domain were transformed to a scale ranged from 0 to 100, where lower scores denoted better health. Haem-A-QoL Total Score was average of all domain scores and ranged from 0 to 100, where lower scores denoted better quality of life. Analysis was performed on ITT population. Here, "number of subjects analysed" = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Month 9

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	31		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.42 (-5.65 to 4.80)	-15.27 (-19.30 to -11.24)		

Statistical analyses

Statistical analysis title	Fitusiran versus BPA on-demand
Comparison groups	Bypassing agents (BPA) on-demand v Fitusiran 80 mg Prophylaxis

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-14.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.37
upper limit	-8.33

Notes:

[7] - ANCOVA model included treatment arm and randomisation strata of number of bleeds (<=10, > 10) as fixed effects, Baseline score as a covariate. Significance threshold was at 0.05.

Secondary: Estimated Annualised Bleeding Rate (ABR) for Treated Bleeds During the Onset Period

End point title	Estimated Annualised Bleeding Rate (ABR) for Treated Bleeds During the Onset Period

End point description:

ABR was annualised number of bleeding episodes during onset period per subject annualised to a 1-year interval of time. A treated bleeding episode was defined as any occurrence of hemorrhage that may required administration of BPA or factor. It started from the first sign of a bleed and ended no more than 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections <=72 hours apart were considered the same bleeding episode. The onset period was defined as time interval from Day 1 to the earlier of Day 28 or the last day of bleeding follow up. This endpoint represents estimated results (i.e., results received by applying NB regression model on data collected during onset period). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 up to Day 28 or up to the last day of bleeding follow up (any day up to Day 28), whichever was the earliest

End point values	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: episodes per subject per year				
number (confidence interval 95%)	25.149 (15.819 to 39.981)	4.426 (2.439 to 8.030)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events

	(TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point 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. Treatment emergent AEs were defined as any AE with onset date after first dose of fitusiran in the fitusiran prophylaxis arm or after Day 1 visit in the BPA on-demand arm. A serious AE (SAE) was defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was a medically important event. Analysis was performed on safety analysis set that included all subjects who received at least 1 dose of study drug or were randomised to on-demand arm, analysed according to the actual treatment received.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to 15 months (i.e. 9 months treatment period + 6-months follow-up)

End point values	BPA on-demand	Fitusiran Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	41		
Units: subjects				
Any TEAE	11	38		
Any TESAE	5	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE data were collected from Baseline (Day 1) up to 15 months (i.e., 9 months treatment period + 6-months follow-up).

Adverse event reporting additional description:

TEAEs: any AE with onset date after first dose of fitusiran in fitusiran prophylaxis arm or after Day 1 visit in the BPA on-demand arm. Analysis done on safety analysis set. Three subjects who were treated with fitusiran but not randomised as per protocol addendum for China, were included in safety analysis for the fitusiran prophylaxis arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Bypassing agents (BPA) on-demand

Reporting group description:

Subjects received On-demand BPAs (use of these agents, as needed, for episodic bleeding episodes, and not on a regular regimen intended to prevent spontaneous bleeding) per Investigator discretion from Day 1 for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Reporting group title	Fitusiran 80 mg Prophylaxis

Reporting group description:

Subjects received fitusiran 80 mg subcutaneously (SC) as prophylaxis once monthly from Day 1, along with the on-demand BPAs (per investigator's discretion and within bleeding dosing guidelines) for treatment of breakthrough bleeding episodes, up to a total of 9 months.

Serious adverse events	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)	7 / 41 (17.07%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tooth Fracture			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Haemorrhage			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	1 / 19 (5.26%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian Vein Thrombosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal Vascular Disorder			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary Colic			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Chronic			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Haemorrhage			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Asymptomatic Covid-19			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma Infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	1 / 41 (2.44%)	
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: 5 %

Non-serious adverse events	Bypassing agents (BPA) on-demand	Fitusiran 80 mg Prophylaxis	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 19 (42.11%)	32 / 41 (78.05%)	
Investigations			
Alanine Aminotransferase Increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	13 / 41 (31.71%)	
occurrences (all)	0	23	
Aspartate Aminotransferase Increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	8 / 41 (19.51%)	
occurrences (all)	0	16	

Blood Alkaline Phosphatase Increased alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 5 / 41 (12.20%) 9	
Fibrin D Dimer Increased alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 3 / 41 (7.32%) 6	
Gamma-Glutamyltransferase Increased alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 6 / 41 (14.63%) 9	
Prothrombin Fragment 1.2 Increased alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 3 / 41 (7.32%) 6	
Transaminases Increased alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 5 / 41 (12.20%) 6	
Nervous system disorders Headache alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1	 6 / 41 (14.63%) 9	
Hypoaesthesia alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1	 0 / 41 (0.00%) 0	
General disorders and administration site conditions Asthenia alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1	 0 / 41 (0.00%) 0	

Pyrexia alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 3 / 41 (7.32%) 3	
Gastrointestinal disorders Abdominal Pain Upper alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 6 / 41 (14.63%) 7	
Constipation alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1	 1 / 41 (2.44%) 1	
Haemorrhoids alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1	 2 / 41 (4.88%) 2	
Skin and subcutaneous tissue disorders Urticaria alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1	 1 / 41 (2.44%) 1	
Musculoskeletal and connective tissue disorders Arthralgia alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 5 / 41 (12.20%) 13	
Back Pain alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1	 1 / 41 (2.44%) 2	
Infections and infestations Asymptomatic Covid-19 alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	1 / 19 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Cystitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Influenza			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Nasopharyngitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 19 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	5	
Pharyngotonsillitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Upper Respiratory Tract Infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 19 (5.26%)	6 / 41 (14.63%)	
occurrences (all)	1	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2018	Following changes were made: 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. Change in address and contact details were also added. The Sanofi Genzyme study code (EFC14768) was added, and the Alnylam study drug code ALN-AT3SC was also updated to the generic drug name fitusiran (SAR439774). Several sections were created or updated to reflect the Sanofi Genzyme environment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported