Clinical trial results:
ATLAS-A/B: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, Without Inhibitory Antibodies to Factor VIII or IX

Summary

EudraCT number	2016-001464-11
Trial protocol	IE BG HU ES PT FR GB DE DK NL IT Outside EU/EEA
Global end of trial date	14 July 2021

Results information

Result version number	v1 (current)
This version publication date	26 January 2022
First version publication date	26 January 2022

Trial information

Trial identification

Sponsor protocol code	EFC14769

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03417245
WHO universal trial number (UTN)	U1111-1251-5229
Other trial identifiers	Alnylam: ALN-AT3SC-004

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	09 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 July 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 factor concentrates, 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	01 March 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	South Africa: 5
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	United States: 7

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	India: 34
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	China: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Malaysia: 6
Worldwide total number of subjects	120
EEA total number of subjects	12

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)	14
Adults (18-64 years)	104
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 64 centres in 19 countries. A total of 177 subjects were screened between 1 March 2018 to 22 May 2020, of which 57 subjects were screen failure. Screen failures were mainly due to presence of a co-existing thrombophilic disorder. In total, 120 subjects were enrolled in the study.

Pre-assignment

Screening details:

120 subjects were randomised in 2:1 ratio to fitusiran prophylaxis and on-demand arms by interactive response system; stratified by the number of bleeding episodes in the 6 months prior to Screening (less than or equal to [<=10] versus [vs] greater than [>]10) and by haemophilia type (haemophilia A or B).

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	Factor On-demand

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Factor 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 open-label fitusiran 80 milligram (mg) administered subcutaneously (SC) as prophylaxis once monthly from Day 1 up to a total of 9 months. Subjects received on-demand factor concentrates (per investigator's discretion and within bleeding dosing guidelines) for the treatment of breakthrough bleeding episodes.

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

Number of subjects in period 1	Factor On-demand	Fitusiran 80 mg Prophylaxis
Started	40	80
Treated	40	79
Completed	37	79
Not completed	3	1
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-
Protocol deviation	1	-

Baseline characteristics

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

Reporting group values	Factor On-demand	Fitusiran 80 mg Prophylaxis	Total
Number of subjects	40	80	120
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	33.6	33.9	
standard deviation	± 13.6	± 14.6	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	40	80	120
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	28	43	71
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	2
White	12	33	45
More than one race	0	2	2
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Factor On-demand

Reporting group description:

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

Reporting group title	Fitusiran 80 mg Prophylaxis

Reporting group description:

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

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): annualised number of bleeding episodes during EP annualised to a 1-year interval of time. Treated Bleeding episode: any occurrence of haemorrhage that required administration of by-passing agents (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 less than or equal to (<=)72 hours apart were considered 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-Day 246). This endpoint presents estimated results (i.e., results received by applying negative binomial [NB] regression model on data collected during EP). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
number (confidence interval 95%)	30.991 (21.114 to 45.487)	3.133 (2.269 to 4.326)		

Statistical analyses

Statistical analysis title	Factor On-demand vs Fitusiran 80 mg Prophylaxis
Comparison groups	Factor On-demand v Fitusiran 80 mg Prophylaxis

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Negative binomial regression mode
Parameter estimate	ABR ratio
Point estimate	0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.159

Notes:

[1] - P-value derived from NB regression model during EP, with treatment arm, number of bleeds in 6 months prior to study (<=10, >10) and haemophilia type (A vs B) as fixed effects. Significance threshold was at 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: annualised number of bleeding episodes during EP annualised to 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 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 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 presents observed results (i.e., descriptive statistics values based on the data collected during EP). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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 provided.

End point values	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))	21.8 (8.4 to 41.0)	0.0 (0.0 to 3.4)		

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 1-year interval of time. Bleeding episode: any occurrence of haemorrhage 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 Day1-Day 246). This endpoint presents estimated results (i.e., results received by applying NB regression model on data collected during TP). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
number (confidence interval 95%)	31.444 (22.995 to 42.999)	4.092 (3.143 to 5.328)		

Statistical analyses

Statistical analysis title	Factor On-demand vs Fitusiran 80 mg Prophylaxis
Comparison groups	Factor On-demand v Fitusiran 80 mg Prophylaxis
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Negative binomial regression model
Parameter estimate	ABR ratio
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.188

Notes:

[3] - P-value derived from NB regression model during TP, with treatment arm, number of bleeds in 6 months prior to study (<=10, >10) and haemophilia type (A vs B) as fixed effects. Significance threshold was at 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: 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 haemorrhage 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: 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 ofbleeding follow-up])(maximum duration of TP: Day 1-Day 246). Endpoint presents observed results(i.e., descriptive statistics values based on data collected during TP). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))	25.2 (11.9 to 43.8)	1.8 (0.0 to 4.5)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Annualised spontaneous bleeding rate for subject during EP: annualised number of spontaneous bleeding episodes during EP annualised to 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 bleed and ended no more than 72 hours after 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 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 presents estimated results (i.e., results received by applying NB regression model on data collected during EP). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
number (confidence interval 95%)	22.036 (14.159 to 34.295)	1.825 (1.237 to 2.692)		

Statistical analyses

Statistical analysis title	Factor On-demand vs Fitusiran 80 mg Prophylaxis
Comparison groups	Factor On-demand v Fitusiran 80 mg Prophylaxis
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Negative binomial regression model
Parameter estimate	ABR ratio
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.141

Notes:

[4] - P-value derived from NB regression model during EP, with treatment arm, number of bleeds in 6 months prior to study (<=10, >10) and haemophilia type (A vs B) as fixed effects. Significance threshold was at 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: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 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. 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:Day 29-Day 246).Endpoint presents observed results(i.e.,descriptive statistics values based on data collected during EP). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))	16.1 (3.4 to 27.6)	0.0 (0.0 to 1.7)		

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: annualised number of bleeding episodes during EP annualised to 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) increasing 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 bleed. 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 the last day of bleeding follow up) (maximum duration of EP: from Day 29-Day 246). This endpoint presents estimated results (i.e., results received by applying NB regression model on data collected during EP). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
number (confidence interval 95%)	23.413 (15.363 to 35.680)	2.282 (1.594 to 3.268)		

Statistical analyses

Statistical analysis title	Factor On-demand vs Fitusiran 80 mg Prophylaxis
Comparison groups	Factor On-demand v Fitusiran 80 mg Prophylaxis

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Negative binomial regression model
Parameter estimate	ABR ratio
Point estimate	0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.059
upper limit	0.161

Notes:

[5] - P-value derived from NB regression model during EP, with treatment arm, number of bleeds in 6 months prior to study (<=10, >10) and haemophilia type (A vs B) as fixed effects. Significance threshold was at 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 during EP: annualised number of 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: characterised by an unusual sensation in joint ("aura") in combination with 1) increasing swelling or warmth over skin, joint, 2) increasing pain, or 3) progressive loss of range of motion or difficulty in using limb. It started from first sign of bleed and ended no more than 72hours 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 performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))	15.9 (4.2 to 33.5)	0.0 (0.0 to 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

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 Score at Month 9

End point description:

Haem-A-QoL: subject-reported questionnaire designed for adult subjects (>=17 years of age) with haemophilia; and consisted of 46 items comprising 10 domains (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with haemophilia, treatment, future, family planning, partnership and sexuality). Scoring for each item was based on a 5-point Likert scale (1= never, 2= rarely,3= sometimes, 4= often, and 5=all the time), and higher scores represented greater impairment. 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 (better health outcome) to 100 (worst health outcome), where lower scores denoted better physical health. Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Month 9

End point values	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	69		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-3.32 (-9.67 to 3.04)	-23.07 (-28.00 to -18.14)		

Statistical analyses

Statistical analysis title	Factor On-demand vs Fitusiran 80 mg Prophylaxis
Comparison groups	Factor On-demand v Fitusiran 80 mg Prophylaxis
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean difference
Point estimate	-19.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27
upper limit	-12.5

Notes:

[6] - Analysis of Covariance (ANCOVA) model included treatment arm, number of bleeds in 6 months prior to study (<=10,>10) and haemophilia type (A vs B) as fixed effects, Baseline score as 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 haemophilia; and consisted of 46 items comprising 10 domains (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with haemophilia, treatment, future, family planning, partnership and sexuality). Scoring for each item was based on a 5-point Likert scale (1= never, 2= rarely,3= sometimes, 4= often, and 5=all the time), and higher scores represent greater impairment. Raw score for each domain were transformed to a scale ranged between 0 and 100, where lower scores denoted better health. Haem-A-QoL Total Score was average of all domain scores and ranged from 0 (better health outcome) to 100 (worst health outcome), where lower scores denoted better physical health. Analysis performed on ITT population. Here, subjects analysed=subjects with available
data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Month 9

End point values	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	69		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-2.62 (-6.27 to 1.03)	-9.68 (-12.51 to -6.86)		

Statistical analyses

Statistical analysis title	Factor On-demand vs Fitusiran 80 mg Prophylaxis
Comparison groups	Factor On-demand v Fitusiran 80 mg Prophylaxis
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [7]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-7.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.23
upper limit	-2.9

Notes:

[7] - ANCOVA model included treatment arm, number of bleeds in 6 months prior to study (<=10,>10) and haemophilia type (A vs B) as fixed effects, Baseline score as 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 1-

yearinterval of time. A treated 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. 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 presents estimated results (i.e., results received by applying NB regression model on data collected during onset period). Analysis performed on ITT population. Here, subjects analysed=subjects with available data.

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	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: episodes per subject per year				
number (confidence interval 95%)	33.389 (25.619 to 43.517)	10.805 (8.143 to 14.337)		

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 1visit in the factor 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-month follow-up)

End point values	Factor On-demand	Fitusiran 80 mg Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	79		
Units: subjects				
Any TEAE	18	62		
Any TESAE	5	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Treatment-emergent AE 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 factor on-demand arm. Analysis was performed on safety analysis set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Factor On-demand

Reporting group description:

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

Reporting group title	Fitusiran 80 mg Prophylaxis

Reporting group description:

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

Serious adverse events	Factor On-demand	Fitusiran 80 mg Prophylaxis	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 40 (12.50%)	5 / 79 (6.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Epidural Haemorrhage			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural Haemorrhage			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Suicidal Ideation			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (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			
Gastroenteritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Factor On-demand	Fitusiran 80 mg Prophylaxis	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 40 (20.00%)	45 / 79 (56.96%)	

Investigations			
Alanine Aminotransferase Increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	18 / 79 (22.78%)	
occurrences (all)	1	20	
Aspartate Aminotransferase Increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 40 (5.00%)	6 / 79 (7.59%)	
occurrences (all)	2	7	
Blood Bilirubin Increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	4 / 40 (10.00%)	3 / 79 (3.80%)	
occurrences (all)	4	3	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	5 / 79 (6.33%)	
occurrences (all)	0	6	
Gastrointestinal disorders			
Abdominal Pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	6 / 79 (7.59%)	
occurrences (all)	1	6	
Abdominal Pain Upper			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	5	
Gastritis			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	1 / 40 (2.50%)	5 / 79 (6.33%)	
occurrences (all)	1	7	
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	5 / 79 (6.33%)	
occurrences (all)	0	5	
Cough			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	6 / 79 (7.59%)	
occurrences (all)	0	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 40 (2.50%)	5 / 79 (6.33%)	
occurrences (all)	1	6	
Infections and infestations			
Nasopharyngitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 40 (7.50%)	7 / 79 (8.86%)	
occurrences (all)	3	7	
Upper Respiratory Tract Infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 40 (0.00%)	9 / 79 (11.39%)	
occurrences (all)	0	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2017	Following changes were made: 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 factor 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, revision of the recommendations for the management of sepsis, and inclusion of additional exploratory laboratory assessments.
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. The Sanofi Genzyme study code (EFC14768) was added, and the Alnylam study drug code ALNAT3SC 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