



## 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)                          | EMA-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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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 ( $\leq 10$  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                              |
| <b>Arm title</b>             | 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.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b>      | 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<br>Units: Subjects            |                                  |                             |       |
| Age continuous<br>Units: years                |                                  |                             |       |
| arithmetic mean                               | 31.5                             | 26.8                        |       |
| standard deviation                            | ± 13.1                           | ± 9.8                       | -     |
| Gender categorical<br>Units: Subjects         |                                  |                             |       |
| Female  | 0                                | 0                           | 0     |
| Male  | 19                               | 38                          | 57    |
| Race/Ethnicity, Customized<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 ( $\leq$ ) 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:<br>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)      |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup>  |
| 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 ( $\leq 10, > 10$ ) 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 <sup>[2]</sup> |
|-----------------|--|

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.  $ABR = \text{number of bleeding episodes during EP} / \text{total number of days during EP} \times 365.25$ . 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  $\leq 72$  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  $\leq$  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 <sup>[3]</sup>            |
| 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 ( $\leq 10, > 10$ ) 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  $\leq 72$  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 ( $\pm$ 15.4)               | 2.0 ( $\pm$ 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 $\leq 72$ 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                                 | $< 0.0001$ <sup>[4]</sup>                                      |
| 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 ( $\leq 10, > 10$ ) 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 |
|-----------------|---|

## 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  $\leq 72$  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 ( $\pm$ 14.9)               | 0.9 ( $\pm$ 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 <sup>[5]</sup>  |
| 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 ( $\leq 10, > 10$ ) 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 ( $\geq 17$  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 <sup>[6]</sup>           |
| 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 ( $\leq 10$ ,  $> 10$ ) 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 ( $\geq 17$  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 <sup>[7]</sup> |
| 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 ( $\leq 10$ ,  $> 10$ ) 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  $\leq 72$  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 |
|-----------------|---|



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 %

| <b>Non-serious adverse events</b>                     | 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                          |  |

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

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

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                 | 1 / 19 (5.26%) | 0 / 41 (0.00%)  |  |
| occurrences (all)                           | 1              | 0               |  |
| Cystitis                                    |                |                 |  |
| alternative dictionary used:<br>MedDRA 24.0 |                |                 |  |
| subjects affected / exposed                 | 1 / 19 (5.26%) | 1 / 41 (2.44%)  |  |
| occurrences (all)                           | 1              | 1               |  |
| Influenza                                   |                |                 |  |
| alternative dictionary used:<br>MedDRA 24.0 |                |                 |  |
| subjects affected / exposed                 | 0 / 19 (0.00%) | 3 / 41 (7.32%)  |  |
| occurrences (all)                           | 0              | 3               |  |
| Nasopharyngitis                             |                |                 |  |
| alternative dictionary used:<br>MedDRA 24.0 |                |                 |  |
| subjects affected / exposed                 | 0 / 19 (0.00%) | 3 / 41 (7.32%)  |  |
| occurrences (all)                           | 0              | 5               |  |
| Pharyngotonsillitis                         |                |                 |  |
| alternative dictionary used:<br>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:<br>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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported