



## Clinical trial results:

### A Multicenter, Open-label Extension Study to Evaluate the Long-term Safety and Clinical Activity of Subcutaneously Administered ALN-AS1 in Patients with Acute Intermittent Porphyria who have Completed a Previous Clinical Study with ALN-AS1

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-002638-54   |
| Trial protocol           | SE GB            |
| Global end of trial date | 05 November 2021 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 21 November 2022 |
| First version publication date | 21 November 2022 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | ALN-AS1-002 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02949830 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Alnylam Pharmaceuticals, Inc.   |
| Sponsor organisation address | 300 Third Street, Cambridge, United States, 02142   |
| Public contact               | Clinical Trial Information Line, Alnylam Pharmaceuticals Inc, + 8772569526, clinicaltrials@alnylam.com  |
| Scientific contact           | Clinical Trial Information Line, Alnylam Pharmaceuticals Inc, +1 8772569526, clinicaltrials@alnylam.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 05 November 2021 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 05 November 2021 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to determine the long-term safety, tolerability and pharmacokinetics of givosiran (ALN-AS1) in AIP patients who completed study ALN-AS1-001.

Protection of trial subjects:

The Investigator ensured that each patient was provided full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. The patient was also notified that they were free to discontinue the study at any time. The patient was given the opportunity to ask questions and was allowed time to consider the information provided. The patient's signed and dated IRB/IEC-approved informed consent was obtained before any study procedures were conducted. The Investigator maintained the original signed ICF, and a copy was given to the patient. All active patients signed an updated ICF if revisions were made to the ICF during the course of the study.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 03 October 2016 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Sweden: 6         |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | United States: 9  |
| Worldwide total number of subjects   | 16                |
| EEA total number of subjects         | 6                 |

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)                 | 0 |

|                      |    |
|----------------------|----|
| Adults (18-64 years) | 16 |
| From 65 to 84 years  | 0  |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients with acute intermittent porphyria (AIP) were enrolled at five sites in Sweden, United Kingdom and the United States.

### Pre-assignment

Screening details:

Patients who completed parent study ALN-AS1-001 (NCT02452372) and met all eligibility criteria for this study (ALN-AS1-002) were enrolled.

### Period 1

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

### Arms

|           |           |
|-----------|-----------|
| Arm title | Givosiran |
|-----------|-----------|

Arm description:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Givosiran              |
| Investigational medicinal product code |                        |
| Other name                             | GIVLAARI, ALN-AS1      |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

| Number of subjects in period 1 | Givosiran |
|--------------------------------|-----------|
| Started                        | 16        |
| Completed                      | 14        |
| Not completed                  | 2         |
| Adverse event, non-fatal       | 1         |
| Withdrawal by Subject          | 1         |

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Givosiran |
|-----------------------|-----------|

Reporting group description:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

| Reporting group values                             | Givosiran | Total |  |
|--|-----------|-------|--|
| Number of subjects                                 | 16        | 16    |  |
| Age categorical                                    |           |       |  |
| Units: Subjects                                    |           |       |  |
| In utero   | 0         | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0         | 0     |  |
| Newborns (0-27 days)                               | 0         | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0         | 0     |  |
| Children (2-11 years)                              | 0         | 0     |  |
| Adolescents (12-17 years)                          | 0         | 0     |  |
| Adults (18-64 years)                               | 16        | 16    |  |
| From 65-84 years                                   | 0         | 0     |  |
| 85 years and over                                  | 0         | 0     |  |
| Age continuous                                     |           |       |  |
| Units: years                                       |           |       |  |
| arithmetic mean                                    | 37.4      |       |  |
| standard deviation                                 | ± 12.0    | -     |  |
| Gender categorical                                 |           |       |  |
| Units: Subjects                                    |           |       |  |
| Female   | 14        | 14    |  |
| Male   | 2         | 2     |  |
| Race   |           |       |  |
| Units: Subjects                                    |           |       |  |
| Asian  | 1         | 1     |  |
| Black or African American                          | 2         | 2     |  |
| White  | 13        | 13    |  |
| Ethnicity  |           |       |  |
| Units: Subjects                                    |           |       |  |
| Not Hispanic or Latino                             | 15        | 15    |  |
| Not Reported                                       | 1         | 1     |  |

## End points

### End points reporting groups

|   |           |
|---|-----------|
| Reporting group title   | Givosiran |
| Reporting group description:<br>At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM. |           |

### Primary: Percentage of Participants with Adverse Events (AEs)

|   |   |
|---|---|
| End point title   | Percentage of Participants with Adverse Events (AEs) <sup>[1]</sup> |
| End point description:<br>An AE is any untoward medical occurrence in a participant or clinical investigational patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.                              |   |
| Statistical Analysis Set (SAS): All patients who received any amount of study drug.   |   |
| End point type  | Primary   |
| End point timeframe:<br>Through Month 49  |   |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: As unit is percentage of participants, no statistical analysis is needed. |   |

| End point values                  | Givosiran       |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 16              |  |  |  |
| Units: percentage of participants |                 |  |  |  |
| number (not applicable)           | 100             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Delta-aminolevulinic Acid (ALA) as Measured by Percent Decrease From Baseline

|  |   |
|--|---|
| End point title  | The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Delta-aminolevulinic Acid (ALA) as Measured by Percent Decrease From Baseline |
| End point description:<br>The PD effect of givosiran was evaluated by spot urine ALA levels normalized to spot urine creatinine levels.<br><br>Patients from the PD Analysis Set (all patients who received any amount of study drug and who had at least 1 post-dose blood sample for PD), who were treated with givosiran 2.5 mg/kg SC injection QM. Values that occurred during a porphyria attack were excluded as a means of controlling for potential confounding by hemin. Overall number of participants analyzed is the number of participants available at the given time point. |   |
| End point type   | Secondary   |

End point timeframe:

Baseline; Month 48

| End point values                 | Givosiran             |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| Subject group type               | Reporting group       |  |  |  |
| Number of subjects analysed      | 9                     |  |  |  |
| Units: percent decrease          |                       |  |  |  |
| arithmetic mean (standard error) | 92.531 ( $\pm$ 1.879) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Porphobilinogen (PBG) as Measured by Percent Decrease From Baseline

|                 |   |
|-----------------|---|
| End point title | The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Porphobilinogen (PBG) as Measured by Percent Decrease From Baseline |
|-----------------|---|

End point description:

The PD effect of givosiran was evaluated by spot urine PBG levels normalized to spot urine creatinine levels.

Patients from the PD Analysis Set (all patients who received any amount of study drug and who had at least 1 post-dose blood sample for PD), who were treated with givosiran 2.5 mg/kg SC injection QM. Values that occurred during a porphyria attack were excluded as a means of controlling for potential confounding by hemin. Overall number of participants analyzed is the number of participants available at the given time point.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline; Month 48

| End point values                 | Givosiran             |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| Subject group type               | Reporting group       |  |  |  |
| Number of subjects analysed      | 9                     |  |  |  |
| Units: percent decrease          |                       |  |  |  |
| arithmetic mean (standard error) | 94.194 ( $\pm$ 2.617) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Annualized Rate of Composite Porphyria Attacks

|   |  |
|---|--|
| End point title   | Annualized Rate of Composite Porphyria Attacks |
| End point description:  |  |
| <p>Porphyria attacks were defined as meeting all of the following criteria: an acute episode of neurovisceral pain in the abdomen, back, chest, extremities and/or limbs, no other medically determined cause, and required treatment with intravenous (IV) dextrose or hemin, carbohydrates, or analgesics, or other medications such as antiemetics at a dose or frequency beyond the participant's usual daily porphyria management. Composite porphyria attacks included porphyria attacks that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home. The annualized attack rate (AAR) was calculated as the number of composite porphyria attacks/total person-years.</p> |  |
| SAS: All patients who received any amount of study drug.  |  |
| End point type  | Secondary                                      |
| End point timeframe:  |  |
| Through Month 48  |  |

|                                  |                 |  |  |  |
|----------------------------------|-----------------|--|--|--|
| <b>End point values</b>          | Givosiran       |  |  |  |
| Subject group type               | Reporting group |  |  |  |
| Number of subjects analysed      | 16              |  |  |  |
| Units: annualized attack rate    |                 |  |  |  |
| arithmetic mean (standard error) | 0.4 (± 1.1)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change in Annualized Days of Hemin Use

|  |  |
|--|--|
| End point title  | Percent Change in Annualized Days of Hemin Use |
| End point description:   |  |
| <p>The percent change in hemin use was calculated as the mean annualized days of hemin use during the study compared with the mean annualized days of hemin use during the Run-in Period. A negative change from Baseline indicates a reduction in annualized days of hemin use.</p> |  |
| End point type   | Secondary                                      |
| End point timeframe:   |  |
| Through Month 49   |  |

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Givosiran       |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 16              |  |  |  |
| Units: percent change       |                 |  |  |  |
| number (not applicable)     | -97.3           |  |  |  |

## Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs with onset after first administration of study drug through end of exposure, or any AE that was present at Baseline but worsened in severity or subsequently considered drug-related by the Investigator (up to approximately 52 months)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Givosiran |
|-----------------------|-----------|

Reporting group description:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

| Serious adverse events                               | Givosiran       |  |  |
|--|-----------------|--|--|
| Total subjects affected by serious adverse events    |                 |  |  |
| subjects affected / exposed                          | 7 / 16 (43.75%) |  |  |
| number of deaths (all causes)                        | 0               |  |  |
| number of deaths resulting from adverse events       | 0               |  |  |
| Injury, poisoning and procedural complications       |                 |  |  |
| Forearm fracture                                     |                 |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Lower limb fracture                                  |                 |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vascular disorders                                   |                 |  |  |
| Deep vein thrombosis                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pyrexia   |                 |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Immune system disorders                         |                 |  |  |
| Anaphylactic reaction                           |                 |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 16 (12.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Mental status changes                           |                 |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Synovitis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Clostridium difficile colitis                   |                 |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory tract infection                     |                 |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 16 (6.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sinusitis bacterial                             |                |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tonsillitis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 16 (6.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Givosiran         |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 16 / 16 (100.00%) |  |  |
| Vascular disorders                                    |                   |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed                           | 4 / 16 (25.00%)   |  |  |
| occurrences (all)                                     | 5                 |  |  |
| Hypotension   |                   |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Superficial vein prominence                           |                   |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Asthenia  |                   |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Chest pain  |                   |  |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Chills  |                   |  |  |

|                               |                 |  |  |
|-------------------------------|-----------------|--|--|
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Discomfort                    |                 |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Facial pain                   |                 |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Fatigue                       |                 |  |  |
| subjects affected / exposed   | 7 / 16 (43.75%) |  |  |
| occurrences (all)             | 12              |  |  |
| Feeling abnormal              |                 |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Injection site bruising       |                 |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Injection site discolouration |                 |  |  |
| subjects affected / exposed   | 2 / 16 (12.50%) |  |  |
| occurrences (all)             | 9               |  |  |
| Injection site dryness        |                 |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Injection site erythema       |                 |  |  |
| subjects affected / exposed   | 6 / 16 (37.50%) |  |  |
| occurrences (all)             | 29              |  |  |
| Injection site indentation    |                 |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Injection site pain           |                 |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  |  |  |
| occurrences (all)             | 1               |  |  |
| Injection site pruritus       |                 |  |  |
| subjects affected / exposed   | 4 / 16 (25.00%) |  |  |
| occurrences (all)             | 11              |  |  |
| Injection site rash           |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 5               |  |  |
| Injection site swelling     |                 |  |  |
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 6               |  |  |
| Injection site urticaria    |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Malaise                     |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Oedema peripheral           |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pain                        |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Peripheral swelling         |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pyrexia                     |                 |  |  |
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 5               |  |  |
| Immune system disorders     |                 |  |  |
| Allergy to animal           |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Drug hypersensitivity       |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hypersensitivity            |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Oral allergy syndrome       |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |

|   |                       |  |  |
|---|-----------------------|--|--|
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)    | 1 / 16 (6.25%)<br>1   |  |  |
| Reproductive system and breast disorders                                |                       |  |  |
| Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)       | 3 / 16 (18.75%)<br>4  |  |  |
| Menorrhagia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 16 (12.50%)<br>16 |  |  |
| Metrorrhagia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 16 (6.25%)<br>1   |  |  |
| Oligomenorrhoea<br>subjects affected / exposed<br>occurrences (all)     | 1 / 16 (6.25%)<br>1   |  |  |
| Respiratory, thoracic and mediastinal disorders                         |                       |  |  |
| Allergic bronchitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1   |  |  |
| Asthma<br>subjects affected / exposed<br>occurrences (all)              | 2 / 16 (12.50%)<br>2  |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)               | 3 / 16 (18.75%)<br>4  |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)            | 3 / 16 (18.75%)<br>3  |  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 16 (6.25%)<br>6   |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 4 / 16 (25.00%)<br>7  |  |  |
| Pharyngeal erythema   |                       |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Throat irritation                            |                 |  |  |
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Psychiatric disorders                        |                 |  |  |
| Anxiety                                      |                 |  |  |
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Attention deficit hyperactivity disorder     |                 |  |  |
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Insomnia                                     |                 |  |  |
| subjects affected / exposed                  | 2 / 16 (12.50%) |  |  |
| occurrences (all)                            | 2               |  |  |
| Panic attack                                 |                 |  |  |
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Investigations                               |                 |  |  |
| Alanine aminotransferase increased           |                 |  |  |
| subjects affected / exposed                  | 2 / 16 (12.50%) |  |  |
| occurrences (all)                            | 4               |  |  |
| Albumin urine present                        |                 |  |  |
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Anticoagulation drug level below therapeutic |                 |  |  |
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Aspartate aminotransferase increased         |                 |  |  |
| subjects affected / exposed                  | 2 / 16 (12.50%) |  |  |
| occurrences (all)                            | 5               |  |  |
| Bilirubin conjugated increased               |                 |  |  |
| subjects affected / exposed                  | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                            | 1               |  |  |
| Blood bilirubin increased                    |                 |  |  |



|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed              | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Blood creatinine increased               |                 |  |  |
| subjects affected / exposed              | 2 / 16 (12.50%) |  |  |
| occurrences (all)                        | 2               |  |  |
| Blood homocysteine increased             |                 |  |  |
| subjects affected / exposed              | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Blood sodium decreased                   |                 |  |  |
| subjects affected / exposed              | 2 / 16 (12.50%) |  |  |
| occurrences (all)                        | 2               |  |  |
| C-reactive protein increased             |                 |  |  |
| subjects affected / exposed              | 2 / 16 (12.50%) |  |  |
| occurrences (all)                        | 2               |  |  |
| Carbon dioxide increased                 |                 |  |  |
| subjects affected / exposed              | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Coronavirus test positive                |                 |  |  |
| subjects affected / exposed              | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Creatinine urine increased               |                 |  |  |
| subjects affected / exposed              | 2 / 16 (12.50%) |  |  |
| occurrences (all)                        | 2               |  |  |
| Gamma-glutamyltransferase increased      |                 |  |  |
| subjects affected / exposed              | 3 / 16 (18.75%) |  |  |
| occurrences (all)                        | 3               |  |  |
| Glomerular filtration rate decreased     |                 |  |  |
| subjects affected / exposed              | 3 / 16 (18.75%) |  |  |
| occurrences (all)                        | 7               |  |  |
| International normalised ratio increased |                 |  |  |
| subjects affected / exposed              | 4 / 16 (25.00%) |  |  |
| occurrences (all)                        | 5               |  |  |
| Lipase increased                         |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                    | 4 / 16 (25.00%) |  |  |
| occurrences (all)                              | 4               |  |  |
| Liver function test increased                  |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Protein urine present                          |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Prothrombin level increased                    |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Transaminases increased                        |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Urine ketone body present                      |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Urine output decreased                         |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Injury, poisoning and procedural complications |                 |  |  |
| Arthropod sting                                |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Fall   |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Foot fracture                                  |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Humerus fracture                               |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Procedural pain                                |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Rib fracture                |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Venomous sting              |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Cardiac disorders           |                 |  |  |
| Palpitations                |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Nervous system disorders    |                 |  |  |
| Dizziness                   |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Dysaesthesia                |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Headache                    |                 |  |  |
| subjects affected / exposed | 5 / 16 (31.25%) |  |  |
| occurrences (all)           | 19              |  |  |
| Hypoaesthesia               |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Migraine                    |                 |  |  |
| subjects affected / exposed | 4 / 16 (25.00%) |  |  |
| occurrences (all)           | 10              |  |  |
| Neuropathy peripheral       |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Paraesthesia                |                 |  |  |
| subjects affected / exposed | 3 / 16 (18.75%) |  |  |
| occurrences (all)           | 4               |  |  |
| Tremor                      |                 |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1   |  |  |
| Blood and lymphatic system disorders<br>Neutrophilia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1   |  |  |
| Ear and labyrinth disorders<br>Cerumen impaction<br>subjects affected / exposed<br>occurrences (all)<br><br>Ear haemorrhage<br>subjects affected / exposed<br>occurrences (all)<br><br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1<br><br>1 / 16 (6.25%)<br>1<br><br>1 / 16 (6.25%)<br>1                             |  |  |
| Eye disorders<br>Conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all)<br><br>Eye pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Eye pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Swelling of eyelid<br>subjects affected / exposed<br>occurrences (all) | 2 / 16 (12.50%)<br>2<br><br>1 / 16 (6.25%)<br>1<br><br>1 / 16 (6.25%)<br>3<br><br>1 / 16 (6.25%)<br>2 |  |  |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain lower  | 1 / 16 (6.25%)<br>1<br><br>6 / 16 (37.50%)<br>19  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed            | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Abdominal pain upper                   |                 |  |  |
| subjects affected / exposed            | 3 / 16 (18.75%) |  |  |
| occurrences (all)                      | 4               |  |  |
| Constipation                           |                 |  |  |
| subjects affected / exposed            | 2 / 16 (12.50%) |  |  |
| occurrences (all)                      | 4               |  |  |
| Diarrhoea                              |                 |  |  |
| subjects affected / exposed            | 4 / 16 (25.00%) |  |  |
| occurrences (all)                      | 7               |  |  |
| Dyspepsia                              |                 |  |  |
| subjects affected / exposed            | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                      | 3               |  |  |
| Irritable bowel syndrome               |                 |  |  |
| subjects affected / exposed            | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Nausea                                 |                 |  |  |
| subjects affected / exposed            | 8 / 16 (50.00%) |  |  |
| occurrences (all)                      | 26              |  |  |
| Stomatitis                             |                 |  |  |
| subjects affected / exposed            | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Teething                               |                 |  |  |
| subjects affected / exposed            | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Vomiting                               |                 |  |  |
| subjects affected / exposed            | 4 / 16 (25.00%) |  |  |
| occurrences (all)                      | 10              |  |  |
| Skin and subcutaneous tissue disorders |                 |  |  |
| Acne                                   |                 |  |  |
| subjects affected / exposed            | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Alopecia                               |                 |  |  |
| subjects affected / exposed            | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                      | 1               |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Angioedema<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1  |  |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)  | 2 / 16 (12.50%)<br>2 |  |  |
| Palmar erythema<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>3  |  |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)  | 3 / 16 (18.75%)<br>5 |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 3 / 16 (18.75%)<br>4 |  |  |
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>3  |  |  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)   | 2 / 16 (12.50%)<br>3 |  |  |
| Renal and urinary disorders<br>Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 16 (12.50%)<br>2 |  |  |
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)  | 2 / 16 (12.50%)<br>2 |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 3 / 16 (18.75%)<br>3 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 5 / 16 (31.25%)<br>9 |  |  |
| Costochondritis   |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Flank pain                  |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Muscle spasms               |                 |  |  |
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 2               |  |  |
| Musculoskeletal chest pain  |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Myalgia                     |                 |  |  |
| subjects affected / exposed | 5 / 16 (31.25%) |  |  |
| occurrences (all)           | 6               |  |  |
| Neck pain                   |                 |  |  |
| subjects affected / exposed | 3 / 16 (18.75%) |  |  |
| occurrences (all)           | 3               |  |  |
| Pain in extremity           |                 |  |  |
| subjects affected / exposed | 4 / 16 (25.00%) |  |  |
| occurrences (all)           | 5               |  |  |
| Pain in jaw                 |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Tendonitis                  |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Infections and infestations |                 |  |  |
| Bronchitis                  |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Conjunctivitis              |                 |  |  |
| subjects affected / exposed | 1 / 16 (6.25%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Ear infection               |                 |  |  |
| subjects affected / exposed | 3 / 16 (18.75%) |  |  |
| occurrences (all)           | 4               |  |  |

|                                   |                 |  |  |
|-----------------------------------|-----------------|--|--|
| Folliculitis                      |                 |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                 | 1               |  |  |
| Fungal infection                  |                 |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                 | 1               |  |  |
| Gastroenteritis                   |                 |  |  |
| subjects affected / exposed       | 4 / 16 (25.00%) |  |  |
| occurrences (all)                 | 4               |  |  |
| Gastroenteritis viral             |                 |  |  |
| subjects affected / exposed       | 2 / 16 (12.50%) |  |  |
| occurrences (all)                 | 2               |  |  |
| Influenza                         |                 |  |  |
| subjects affected / exposed       | 3 / 16 (18.75%) |  |  |
| occurrences (all)                 | 4               |  |  |
| Nasopharyngitis                   |                 |  |  |
| subjects affected / exposed       | 8 / 16 (50.00%) |  |  |
| occurrences (all)                 | 17              |  |  |
| Pharyngitis streptococcal         |                 |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                 | 1               |  |  |
| Sinusitis                         |                 |  |  |
| subjects affected / exposed       | 2 / 16 (12.50%) |  |  |
| occurrences (all)                 | 2               |  |  |
| Skin infection                    |                 |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                 | 1               |  |  |
| Tonsillitis                       |                 |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                 | 1               |  |  |
| Upper respiratory tract infection |                 |  |  |
| subjects affected / exposed       | 3 / 16 (18.75%) |  |  |
| occurrences (all)                 | 4               |  |  |
| Urinary tract infection           |                 |  |  |
| subjects affected / exposed       | 2 / 16 (12.50%) |  |  |
| occurrences (all)                 | 3               |  |  |



|  |                       |  |  |
|--|-----------------------|--|--|
| Varicella<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1   |  |  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1   |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 3 / 16 (18.75%)<br>14 |  |  |
| Gluten sensitivity<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 16 (6.25%)<br>1   |  |  |
| Type 2 diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 16 (6.25%)<br>1   |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 10 November 2016 | Amendment 1 - The primary purpose for this protocol amendment is to clarify that based on review of data from the ongoing ALN-AS1-001 study, the Safety Review Committee (SRC) has determined the study starting dose and dosing regimen for administration in study ALN-AS1-002 is to be 5.0 mg/kg administered every 3 months. Additionally, minor changes were made to schedules of assessment to increase consistency and clarity.   |
| 01 December 2016 | <p>Amendment 2 - The primary purpose of this amendment is to implement additional safety monitoring; specifically to require lipase monitoring and review of recent clinical laboratory results prior to dosing. These changes are being made in accordance with the study's Safety Review Committee recommendation pursuant to an unlikely related SAE of hemorrhagic pancreatitis with fatal outcome.</p> <p>Additionally, out of date text describing the nonclinical and clinical experience with ALN-AS1 has been removed and replaced with a reference to the current Investigator's Brochure, which has been updated to include a description of the aforementioned unlikely related fatal SAE.</p> |
| 03 February 2017 | Amendment 3 - The purpose of this amendment is to update the risk-benefit assessment of the study protocol to align with the current Investigator's Brochure, to add regular monitoring of prothrombin time (PT), International Normalized Ratio (INR), and c-reactive protein (CRP), and to clarify the timing of the review of clinical laboratory assessments prior to scheduled dosing.  |
| 02 August 2017   | <p>Amendment 4 - This protocol is being amended to update the electrocardiogram (ECG) assessments to obtain triplicate 12-lead ECGs using central equipment and paired with plasma PK at times corresponding to nominal maximum concentration (C<sub>max</sub>).</p> <p>Also, Schedule of Assessments footnotes and related text were updated to define the visit range in which previously noted predose interpretation of hematology, coagulation, and chemistry test results are required.</p>  |

|               |   |
|---------------|---|
| 03 May 2018   | <p>Amendment 5 - The purpose of the amendment is to:<br/>Include clinical data on a single case of anaphylactic reaction, information regarding the potential risk for anaphylactic reactions, and provide updated guidance for dosing and monitoring. The event of anaphylactic reaction was previously reported to applicable regulatory authorities and Institutional Review Boards/Ethics Committees.</p> <p>Benefit-Risk Assessment modified to align with potential risks in the Investigator's Brochure. Information on reproductive health moved to Contraceptive Requirements and cytochrome P450 (CYP) inhibition moved to Concomitant Medications.</p> <p>Update guidance and procedures on patient withdrawal from study. Schedule of Assessments footnotes were updated to:<br/>Update end of study visit, early termination visit, and safety follow-up visit timing and assessments.</p> <p>Clarify clinical laboratory testing required prior to dosing.</p> <p>Clarify timing of ECG assessments for patients administered <math>\leq 2.5</math> mg/kg and <math>&gt;2.5</math> mg/kg ALN-AS1 provide the following clarifications:</p> <ul style="list-style-type: none"> <li>o patient withdrawal details regarding subsequent visits and data collection</li> <li>o definition of sexual abstinence</li> <li>o contraception with an intrauterine hormone-releasing system also requires use of a barrier method</li> </ul> |
| 28 May 2019   | <p>Amendment 6 - The primary purpose for this protocol amendment is to provide updated information from a recently completed drug-drug interaction study (ALN-AS1-004) performed in acute intermittent porphyria (AIP) patients who are asymptomatic high excretors in the concomitant medications section. The results of the study indicated that ALN-AS1 treatment resulted in moderate reduction in CYP1A2 and CYP2D6 activity, weak reduction in CYP3A4 and CYP2C19 activity, and no change in the activity of CYP2C9.</p> <p>This amendment also extends the treatment period to 48 months to continue the study until ALN-AS1 is anticipated to be commercially available in the countries where the study sites are located.</p> <p>Additional updates are being implemented as noted below: clarification that patients may continue to receive ALN-AS1 until it is commercially available in the patient's territory, addition of guidance for serious breaches of protocol, and deletion of Section 11.3, List of Sensitive CYP3A substrates and those with a Narrow Therapeutic Range.</p>  |
| 29 April 2020 | <p>Amendment 7 - The purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter to assure the safety of study participants while minimizing risks to study integrity amid the COVID-19 pandemic. These changes are in line with guidance from both the European Medicines Agency and the United States Food and Drug Administration on the conduct of clinical trials during the COVID-19 pandemic.</p>   |
| 29 March 2021 | <p>Amendment 8 - The purpose of this protocol amendment is to recommend testing of blood homocysteine levels. In addition, it is recommended that patients with increased blood homocysteine levels receive a supplement containing vitamin B6.</p> <p>These recommendations are being made because during ALN-AS1 treatment, increases in blood homocysteine levels have been observed compared to levels before ALN-AS1 treatment. Thus, monitoring for changes in blood homocysteine levels during treatment with ALN-AS1 has been incorporated into the protocol. Blood homocysteine levels may also be increased in patients with acute hepatic porphyria (AHP), vitamin deficiencies, or chronic kidney disease. The clinical relevance of the elevations in blood homocysteine during ALN-AS1 treatment is unknown.</p>  |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported