



## Clinical trial results:

### An Open-Label Study To Evaluate The Efficacy And Safety Of Revusiran In Patients With Transthyretin-Mediated Familial Amyloidotic Polyneuropathy With Disease Progression Post Orthotopic Liver Transplant

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-002603-29   |
| Trial protocol           | SE PT ES GB      |
| Global end of trial date | 06 February 2017 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 21 February 2018 |
| First version publication date | 21 February 2018 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | ALN-TTRSC-005 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02595983 |
| 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               | Investor Relations and Corporate Communications, Alnylam Pharmaceuticals Inc, Investors@alnylam.com |
| Scientific contact           | Chief Medical Officer, Alnylam Pharmaceuticals Inc, 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:

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**Results analysis stage**

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 02 May 2017      |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 06 February 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 06 February 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

Assess the efficacy of revusiran in patients with transthyretin (TTR)-amyloidosis (hATTR amyloidosis) with polyneuropathy, with disease progression post-orthotopic liver transplant (OLT) by evaluating the reduction in serum TTR level compared to baseline.

Protection of trial subjects:

An independent Data Monitoring Committee was implemented for the study and operated under a prespecified charter. The Data Monitoring Committee was responsible for monitoring the progress of the study and the safety of the participants.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 28 December 2015 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Portugal: 3       |
| Country: Number of subjects enrolled | Spain: 2          |
| Country: Number of subjects enrolled | Sweden: 1         |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | France: 3         |
| Country: Number of subjects enrolled | Germany: 2        |
| Worldwide total number of subjects   | 12                |
| EEA total number of subjects         | 12                |

Notes:

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**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)      | 10 |
| From 65 to 84 years       | 2  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 12 patients with hATTR amyloidosis with polyneuropathy who had neuropathy progression following OLT were enrolled and treated in this study.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 12 |
| Number of subjects completed | 12 |

### Period 1

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

### Arms

|           |              |
|-----------|--------------|
| Arm title | All Patients |
|-----------|--------------|

Arm description:

All patients who received at least 1 dose of the study drug

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Revusiran              |
| Investigational medicinal product code | ALN-TTRSC              |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Patients received 5 daily doses of 500 mg revusiran (Days 0 through 4) and a dose of 500 mg on Day 7, followed by once weekly 500 mg doses for the duration of the study, until termination of dosing

| Number of subjects in period 1 | All Patients |
|--------------------------------|--------------|
| Started                        | 12           |
| Completed                      | 8            |
| Not completed                  | 4            |
| Adverse event, serious fatal   | 2            |
| Consent withdrawn by subject   | 1            |
| Adverse event, non-fatal       | 1            |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall Trial |
| Reporting group description: - |               |

| Reporting group values                             | Overall Trial | Total |  |
|----------------------------------------------------|---------------|-------|--|
| Number of subjects                                 | 12            | 12    |  |
| 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)                               | 10            | 10    |  |
| From 65-84 years                                   | 2             | 2     |  |
| 85 years and over                                  | 0             | 0     |  |
| Age continuous                                     |               |       |  |
| Units: years                                       |               |       |  |
| arithmetic mean                                    | 55.8          |       |  |
| standard deviation                                 | ± 8.65        | -     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female                                             | 3             | 3     |  |
| Male                                               | 9             | 9     |  |

### Subject analysis sets

|                                                                 |                 |
|-----------------------------------------------------------------|-----------------|
| Subject analysis set title                                      | Safety          |
| Subject analysis set type                                       | Safety analysis |
| Subject analysis set description:                               |                 |
| All patients who received at least a single dose of study drug. |                 |

| Reporting group values                             | Safety |  |  |
|----------------------------------------------------|--------|--|--|
| Number of subjects                                 | 12     |  |  |
| Age categorical                                    |        |  |  |
| Units: Subjects                                    |        |  |  |
| In utero                                           | 0      |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)                               | 10     |  |  |

|                   |   |  |  |
|-------------------|---|--|--|
| From 65-84 years  | 2 |  |  |
| 85 years and over | 0 |  |  |

  

|                    |        |  |  |
|--------------------|--------|--|--|
| Age continuous     |        |  |  |
| Units: years       |        |  |  |
| arithmetic mean    | 55.8   |  |  |
| standard deviation | ± 8.65 |  |  |
| Gender categorical |        |  |  |
| Units: Subjects    |        |  |  |
| Female             | 3      |  |  |
| Male               | 9      |  |  |

## End points

### End points reporting groups

|                                                                                                      |                 |
|------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title                                                                                | All Patients    |
| Reporting group description:<br>All patients who received at least 1 dose of the study drug          |                 |
| Subject analysis set title                                                                           | Safety          |
| Subject analysis set type                                                                            | Safety analysis |
| Subject analysis set description:<br>All patients who received at least a single dose of study drug. |                 |

### Primary: Serum TTR over 6 months

|                                                                                           |                                        |
|-------------------------------------------------------------------------------------------|----------------------------------------|
| End point title                                                                           | Serum TTR over 6 months <sup>[1]</sup> |
| End point description:<br>Percent reduction from baseline in serum TTR level at 6 months. |                                        |
| End point type                                                                            | Primary                                |
| End point timeframe:<br>6 months                                                          |                                        |

Notes:

[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.

Justification: Limited collection of data due to the Sponsor's decision to terminate the study.

| End point values            | Safety               |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 0 <sup>[2]</sup>     |  |  |  |
| Units: Percentage           |                      |  |  |  |

Notes:

[2] - Limited collection of data due to the Sponsor's decision to terminate the study.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred after the start of study drug administration on Day 0 (Baseline) up to 90 days post modified early termination visit (End of Study)

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety Population |
|-----------------------|-------------------|

Reporting group description:

All patients who received at least 1 dose of study drug

| Serious adverse events                                              | Safety Population |  |  |
|---------------------------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed                                         | 8 / 12 (66.67%)   |  |  |
| number of deaths (all causes)                                       | 2                 |  |  |
| number of deaths resulting from adverse events                      | 2                 |  |  |
| Investigations                                                      |                   |  |  |
| Blood immunoglobulin M increased                                    |                   |  |  |
| subjects affected / exposed                                         | 1 / 12 (8.33%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Adrenal adenoma                                                     |                   |  |  |
| subjects affected / exposed                                         | 1 / 12 (8.33%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Vascular disorders                                                  |                   |  |  |
| Hypotension                                                         |                   |  |  |
| subjects affected / exposed                                         | 1 / 12 (8.33%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Cardiac disorders                                                   |                   |  |  |
| Cardiac arrest                                                      |                   |  |  |



|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 1          |  |  |
| Cardiac failure                                      |                |  |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pericardial effusion                                 |                |  |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Nervous system disorders                             |                |  |  |
| Coma                                                 |                |  |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Hypercapnic coma                                     |                |  |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Loss of consciousness                                |                |  |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Death                                                |                |  |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 1 / 1          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Ascites                                              |                |  |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Dysphagia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea                                          |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting                                        |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Confusional state                               |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Renal failure                                   |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Muscular weakness                               |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Aspergillus infection                           |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyelonephritis acute                            |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Septic shock                                    |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Safety Population |  |  |
|-------------------------------------------------------|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 11 / 12 (91.67%)  |  |  |
| Vascular disorders                                    |                   |  |  |
| Hypotension                                           |                   |  |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Oedema peripheral                                     |                   |  |  |
| subjects affected / exposed                           | 4 / 12 (33.33%)   |  |  |
| occurrences (all)                                     | 6                 |  |  |
| Injection site erythema                               |                   |  |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Injection site haematoma                              |                   |  |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Gait disturbance                                      |                   |  |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Generalised oedema                                    |                   |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Injection site bruising                         |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Secretion discharge                             |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Asthenia                                        |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Malaise                                         |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Reproductive system and breast disorders        |                |  |  |
| Benign prostatic hyperplasia                    |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Cough                                           |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Dysphonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Hypoxia                                         |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Dyspnoea                                        |                |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Psychiatric disorders                           |                |  |  |

|                                                                                  |                      |  |  |
|----------------------------------------------------------------------------------|----------------------|--|--|
| Depression<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 12 (8.33%)<br>1  |  |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 12 (8.33%)<br>1  |  |  |
| Investigations                                                                   |                      |  |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)     | 1 / 12 (8.33%)<br>1  |  |  |
| Prothrombin level decreased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>1  |  |  |
| Blood lactic acid increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>1  |  |  |
| Blood pyruvic acid increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1  |  |  |
| Blood pressure abnormal<br>subjects affected / exposed<br>occurrences (all)      | 1 / 12 (8.33%)<br>1  |  |  |
| Liver function test abnormal<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1  |  |  |
| Injury, poisoning and procedural complications                                   |                      |  |  |
| Thermal burn<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 12 (16.67%)<br>2 |  |  |
| Tooth fracture<br>subjects affected / exposed<br>occurrences (all)               | 1 / 12 (8.33%)<br>1  |  |  |
| Eschar<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 12 (8.33%)<br>1  |  |  |
| Wound                                                                            |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Cardiac disorders           |                 |  |  |
| Cardiac failure             |                 |  |  |
| subjects affected / exposed | 2 / 12 (16.67%) |  |  |
| occurrences (all)           | 2               |  |  |
| Cardiomyopathy              |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Atrial fibrillation         |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Tachycardia                 |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Nervous system disorders    |                 |  |  |
| Headache                    |                 |  |  |
| subjects affected / exposed | 3 / 12 (25.00%) |  |  |
| occurrences (all)           | 4               |  |  |
| Hypoaesthesia               |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Syncope                     |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Speech disorder             |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Aphasia                     |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Paraesthesia                |                 |  |  |
| subjects affected / exposed | 1 / 12 (8.33%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Neuropathy peripheral       |                 |  |  |

|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Peripheral sensorimotor neuropathy   |                 |  |  |
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Somnolence                           |                 |  |  |
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Polyneuropathy                       |                 |  |  |
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Blood and lymphatic system disorders |                 |  |  |
| Macrocytosis                         |                 |  |  |
| subjects affected / exposed          | 3 / 12 (25.00%) |  |  |
| occurrences (all)                    | 3               |  |  |
| Leukopenia                           |                 |  |  |
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Eye disorders                        |                 |  |  |
| Cataract                             |                 |  |  |
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Retinal vein occlusion               |                 |  |  |
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Dry eye                              |                 |  |  |
| subjects affected / exposed          | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Gastrointestinal disorders           |                 |  |  |
| Diarrhoea                            |                 |  |  |
| subjects affected / exposed          | 4 / 12 (33.33%) |  |  |
| occurrences (all)                    | 4               |  |  |
| Nausea                               |                 |  |  |
| subjects affected / exposed          | 3 / 12 (25.00%) |  |  |
| occurrences (all)                    | 5               |  |  |
| Vomiting                             |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 12 (16.67%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Constipation                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 12 (16.67%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Toothache                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Aerophagia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Skin lesion                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pruritus                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Rash                                            |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 3 / 12 (25.00%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Dysuria                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Endocrine disorders                             |                 |  |  |
| Adrenal insufficiency                           |                 |  |  |
| subjects affected / exposed                     | 1 / 12 (8.33%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |



|                                                                             |                      |  |  |
|-----------------------------------------------------------------------------|----------------------|--|--|
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)       | 3 / 12 (25.00%)<br>3 |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)       | 2 / 12 (16.67%)<br>2 |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 12 (8.33%)<br>2  |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)               | 1 / 12 (8.33%)<br>1  |  |  |
| Joint stiffness<br>subjects affected / exposed<br>occurrences (all)         | 1 / 12 (8.33%)<br>1  |  |  |
| Infections and infestations                                                 |                      |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)         | 3 / 12 (25.00%)<br>4 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 12 (16.67%)<br>4 |  |  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 12 (8.33%)<br>1  |  |  |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)             | 1 / 12 (8.33%)<br>1  |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)              | 1 / 12 (8.33%)<br>1  |  |  |
| Metabolism and nutrition disorders                                          |                      |  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)           | 2 / 12 (16.67%)<br>2 |  |  |
| Hyperuricaemia                                                              |                      |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 12 (8.33%) |  |  |
| occurrences (all)           | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 09 March 2016   | The primary purpose for the protocol amendment is to allow for more intensive monitoring of liver function in response to adverse events (AEs) in ongoing and completed studies with revusiran in patients with transthyretin-mediated cardiac amyloidosis.                                                       |
| 12 October 2016 | The primary purpose of Protocol Amendment 3 is to provide guidance for follow-up of patients enrolled in the study following the Sponsor's decision to discontinue study drug dosing in all ongoing revusiran studies as previously communicated to the investigators, ethics committees, and health authorities. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Safety and efficacy conclusions are limited due to Sponsor's decision to terminate the study.

Notes: