



Clinical trial results:

A Phase 2, Open-Label Trial to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics and Exploratory Clinical Activity of ALN-TTRSC in Patients with Transthyretin (TTR) Cardiac Amyloidosis

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2013-002856-33 |
| Trial protocol | GB |
| Global end of trial date | 05 January 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 09 April 2016 |
| First version publication date | 09 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | ALN-TTRSC-002 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01981837 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Alnylam Pharmaceuticals, Inc. |
| Sponsor organisation address | 300 Third Street, Cambridge, MA, United States, 02142 |
| Public contact | Investor Relations & Corporate Communication, Alnylam Pharmaceuticals, Inc., investors@alnylam.com |
| Scientific contact | Senior Vice President, Clinical Development, 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:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 January 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 January 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of multiple doses of ALN-TTRSC (revusiran) in patients with ATTR cardiac amyloidosis.

Protection of trial subjects:

A Safety Review Committee (SRC) was in place for this study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 06 January 2014 |
| 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 | United Kingdom: 10 |
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects | 26 |
| EEA total number of subjects | 10 |

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) | 7 |
| From 65 to 84 years | 19 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 26 patients who met all inclusion criteria and none of the exclusion criteria were enrolled.

Period 1

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

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ALN-TTRSC (revusiran) 5.0 mg/kg |

Arm description:

Patients received 5.0 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses

| | |
|--|------------------------|
| 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:

5.0 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses. Patients received a daily dose of ALN-TTRSC (revusiran) over 5 consecutive days (Days 0, 1, 2, 3, and 4) and then they received once weekly doses of ALN-TTRSC (revusiran) for 5 weeks (Days 7, 14, 21, 28, and 35).

| | |
|------------------|---------------------------------|
| Arm title | ALN-TTRSC (revusiran) 7.5 mg/kg |
|------------------|---------------------------------|

Arm description:

Patients received 7.5 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses

| | |
|--|------------------------|
| 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:

7.5 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses. Patients received a daily dose of ALN-TTRSC (revusiran) over 5 consecutive days (Days 0, 1, 2, 3, and 4) and then they received once weekly doses of ALN-TTRSC (revusiran) for 5 weeks (Days 7, 14, 21, 28, and 35).

| Number of subjects in period 1 | ALN-TTRSC (revusiran) 5.0 mg/kg | ALN-TTRSC (revusiran) 7.5 mg/kg |
|---------------------------------------|---------------------------------------|---------------------------------------|
| Started | 23 | 3 |
| Completed | 23 | 3 |

Baseline characteristics

Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 26 | 26 | |
| 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) | 7 | 7 | |
| From 65-84 years | 19 | 19 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 68.1 | | |
| standard deviation | ± 6.36 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 23 | 23 | |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | ALN-TTRSC (revusiran) 5.0 mg/kg |
| Reporting group description: | |
| Patients received 5.0 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses | |
| Reporting group title | ALN-TTRSC (revusiran) 7.5 mg/kg |
| Reporting group description: | |
| Patients received 7.5 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses | |

Primary: Safety and tolerability of multiple doses of ALN-TTRSC (revusiran) in patients with ATTR cardiac amyloidosis

| | |
|--|---|
| End point title | Safety and tolerability of multiple doses of ALN-TTRSC (revusiran) in patients with ATTR cardiac amyloidosis ^[1] |
| End point description: | |
| The number of patients experiencing adverse events (AEs), serious adverse events (SAEs) and study drug discontinuation (due to any reason) | |
| End point type | Primary |
| End point timeframe: | |
| Up to 90 days post first dose | |

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: No inferential analyses were conducted as the primary endpoint was safety and tolerability. Analyses were descriptive in nature.

| End point values | ALN-TTRSC (revusiran) 5.0 mg/kg | ALN-TTRSC (revusiran) 7.5 mg/kg | | |
|--|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 3 | | |
| Units: patients | | | | |
| At least 1 Treatment Emergent Adverse Event (TEAE) | 17 | 3 | | |
| At least 1 Serious TEAE | 3 | 0 | | |
| Study Drug Discontinuation For Any Reason | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): AUC

| | |
|---|--|
| End point title | Pharmacokinetic parameters of ALN-TTRSC (revusiran): AUC |
| End point description: | |
| Partial area under the plasma concentration-time curve from time 0 to 24 hours (AUC 0-24) and area under the curve from time 0 to the last quantifiable concentration (AUC 0-last) of ALN-TTRSC (revusiran) | |
| End point type | Secondary |

End point timeframe:
Up to 90 days post first dose

| End point values | ALN-TTRSC (revusiran) 5.0 mg/kg | ALN-TTRSC (revusiran) 7.5 mg/kg | | |
|--------------------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 3 | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC 0-24: Day 0 | 9523.2 (± 3606.45) | 16006.2 (± 1728) | | |
| AUC 0-last: Day 0 | 9217.2 (± 3746.44) | 12684.8 (± 6546.56) | | |
| AUC 0-24: Day 4 | 13364.4 (± 6241.06) | 29124 (± 6241.55) | | |
| AUC 0-last: Day 4 | 4310.2 (± 1425.93) | 7547.5 (± 1186.01) | | |
| AUC 0-24: Day 35 | 9960.7 (± 5554.52) | 27122.5 (± 3826.16) | | |
| AUC 0-last: Day 35 | 7853.3 (± 6398.12) | 6102.6 (± 989.08) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum transthyretin (TTR) protein

| | |
|--|-----------------------------------|
| End point title | Serum transthyretin (TTR) protein |
| End point description: | |
| Percent lowering of TTR relative to pretreatment/baseline levels | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 90 days post first dose | |

| End point values | ALN-TTRSC (revusiran) 5.0 mg/kg | ALN-TTRSC (revusiran) 7.5 mg/kg | | |
|---|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 3 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Percent Change of Serum TTR at Day 21 | -80.208 (± 11.2259) | -91.431 (± 4.2603) | | |
| Mean Percent Change of Serum TTR at Day 42 | -83.593 (± 10.9567) | -90.232 (± 5.7909) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): Cmax

| | |
|-----------------|---|
| End point title | Pharmacokinetic parameters of ALN-TTRSC (revusiran): Cmax |
|-----------------|---|

End point description:

Maximum observed plasma concentration (Cmax) of ALN-TTRSC (revusiran)

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

End point timeframe:

Up to 90 days post first dose

| End point values | ALN-TTRSC (revusiran) 5.0 mg/kg | ALN-TTRSC (revusiran) 7.5 mg/kg | | |
|--------------------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 3 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cmax: Day 0 | 814.5 (± 574.57) | 1043 (± 71.842) | | |
| Cmax: Day 4 | 942.9 (± 322.33) | 1503 (± 205.99) | | |
| Cmax: Day 35 | 691 (± 394.14) | 1263 (± 156.95) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): tmax

| | |
|-----------------|---|
| End point title | Pharmacokinetic parameters of ALN-TTRSC (revusiran): tmax |
|-----------------|---|

End point description:

Time of maximum observed plasma concentration (tmax) of ALN-TTRSC (revusiran)

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

End point timeframe:

Up to 90 days

| End point values | ALN-TTRSC (revusiran) 5.0 mg/kg | ALN-TTRSC (revusiran) 7.5 mg/kg | | |
|--------------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 3 | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| tmax: Day 0 | 4.11 (± 2.1618) | 5.3 (± 1.0833) | | |
| tmax: Day 4 | 2.292 (± 1.8866) | 3.317 (± 2.3238) | | |
| tmax: Day 35 | 2.879 (± 2.2485) | 5.272 (± 1.0301) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): CLss/F

| | |
|--|---|
| End point title | Pharmacokinetic parameters of ALN-TTRSC (revusiran): CLss/F |
| End point description: | |
| Systemic clearance (CLss/F) of ALN-TTRSC (revusiran) | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 90 days post first dose | |

| End point values | ALN-TTRSC (revusiran) 5.0 mg/kg | ALN-TTRSC (revusiran) 7.5 mg/kg | | |
|--------------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 3 | | |
| Units: L/h/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| CLss/F: Day 4 | 0.5034 (± 0.34314) | 0.2667 (± 0.064487) | | |
| CLss/F: Day 35 | 0.2602 (± 0.16303) | 0.07163 (± 0.009483) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The Investigator reported all AEs that occurred after the first dose of study drug through the Day 63 or Early Termination visit regardless of their relationship to study drug or clinical significance.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | Overall Trial | | |
|--|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Implantable defibrillator insertion | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| 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 %

| Non-serious adverse events | Overall Trial | | |
|--|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 20 / 26 (76.92%) | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 3 | | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 3 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all) Injection site bruising subjects affected / exposed occurrences (all) Injection site rash subjects affected / exposed occurrences (all) | 4 / 26 (15.38%) 4 4 / 26 (15.38%) 6 2 / 26 (7.69%) 3 2 / 26 (7.69%) 2 | | |
| Eye disorders Vision blurred subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|----------------------|--|--|
| Nausea subjects affected / exposed occurrences (all) | 3 / 26 (11.54%) 4 | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 4 / 26 (15.38%) 4 | | |
| Dysphonia subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 4 / 26 (15.38%) 4 | | |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 7 / 26 (26.92%) 8 | | |
| Muscle spasms subjects affected / exposed occurrences (all) | 3 / 26 (11.54%) 4 | | |
| Back pain subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |
| Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 30 September 2013 | Protocol Amendment 1 <ul style="list-style-type: none">• The method of acceptable contraception for study participants was revised to reflect MHRA guidelines |
| 16 October 2013 | Protocol Amendment 2 <ul style="list-style-type: none">• Increased patient numbers from 12 to 15• Study drug dose decreased from 7.5 mg/kg to 5.0 mg/kg |
| 21 January 2014 | Protocol Amendment 3 <ul style="list-style-type: none">• Changes to timings of pharmacokinetic blood draws• Measurement of vitamin A serum levels added to the Schedule of Assessments for the Day 35 visit |
| 20 May 2014 | Protocol Amendment 4 <ul style="list-style-type: none">• The number of patients was increased to approximately 25 patients• Inclusion Criterion #2 was changed to include only cardiac amyloidosis patients with a TTR mutation• Exclusion Criterion #5 was modified to exclude patients with vitamin A levels consistent with vitamin A deficiency (ie, <20 µg/dL) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported