# Clinical trial results:
# A Phase 1/2, Randomized, Single-Blind, Placebo-Controlled, Single-Ascending, and Multiple-Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-AAT in Healthy Adult Subjects and Patients with ZZ Type Alpha 1 Antitrypsin Deficiency Liver Disease

## Summary

| | |
|---|---|
| EudraCT number | 2015-001297-18 |
| Trial protocol | GB |
| Global end of trial date | 03 January 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 13 January 2019 |
| First version publication date | 13 January 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | ALN-AAT-001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02503683 |
| 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 and Corporate Communications, Alnylam Pharmaceuticals, Inc, 001 8663300326, Investors@alnylam.com |
| Scientific contact | Chief Medical Officer, Alnylam Pharmaceuticals, Inc, 001 8663300326, medinfo@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 | 03 January 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 January 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of single or multiple doses of ALN-AAT when administered to healthy adult subjects and patients with homozygous ZZ type AAT deficiency liver disease (PiZZ patients).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 July 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 24 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 26 |
| Worldwide total number of subjects | 26 |
| EEA total number of subjects | 26 |

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) | 26 |
| From 65 to 84 years | 0 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

One clinical study site in the United Kingdom participated in this study.

### Pre-assignment

Screening details:

Twenty six healthy subjects were enrolled in this study. In Part A, single ascending dose (SAD), twenty healthy subjects were dosed and in Part B, multiple ascending dose (MAD), six healthy subjects were dosed.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Part A: SAD: Placebo |

Arm description:

A single dose of matching placebo was administered.

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

Dosage and administration details:

Matching placebo (normal saline: 0.9% sodium chloride [NaCl]) was administered subcutaneously (SC) on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| | |
|---|---|
| **Arm title** | Part A: SAD: ALN-AAT 0.1 mg/kg |

Arm description:

A single dose of 0.1 mg/kg ALN-AAT was administered.

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

Dosage and administration details:

ALN-AAT was administered SC on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| | |
|---|---|
| **Arm title** | Part A: SAD: ALN-AAT 0.3 mg/kg |

Arm description:

A single dose of 0.3 mg/kg ALN-AAT was administered.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | ALN-AAT |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

ALN-AAT was administered SC on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| | |
|---|---|
| **Arm title** | Part A: SAD: ALN-AAT 1.0 mg/kg |

Arm description:

A single dose of 1.0 mg/kg ALN-AAT was administered.

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

Dosage and administration details:

ALN-AAT was administered SC on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| | |
|---|---|
| **Arm title** | Part A: SAD: ALN-AAT 3.0 mg/kg |

Arm description:

A single dose of 3.0 mg/kg ALN-AAT was administered.

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

Dosage and administration details:

ALN-AAT was administered SC on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| | |
|---|---|
| **Arm title** | Part A: SAD: ALN-AAT 6.0 mg/kg |

Arm description:

A single dose of 6.0 mg/kg ALN-AAT was administered.

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

Dosage and administration details:

ALN-AAT was administered SC on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| | |
|---|---|
| **Arm title** | Part B: MAD: Placebo |

Arm description:

Multiple doses (once every 4 weeks) of matching placebo were administered.

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

Dosage and administration details:

Matching placebo (normal saline: 0.9% sodium chloride [NaCl]) was administered SC on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| **Arm title** | Part B: MAD: ALN-AAT 1.0 mg/kg |
|---|---|

Arm description:

Multiple doses (once every 4 weeks) of 1.0 mg/kg ALN-AAT were administered.

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

Dosage and administration details:

ALN-AAT was administered SC on Day 0 for Part A: SAD and on Days 0, 28, 56, and 84 for Part B: MAD.

| **Number of subjects in period 1** | Part A: SAD: Placebo | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg |
|---|---|---|---|
| Started | 5 | 3 | 3 |
| Completed | 5 | 3 | 3 |
| Not completed | 0 | 0 | 0 |
| Reason not specified | - | - | - |
| Lost to follow-up | - | - | - |
| Withdrawal by subject | - | - | - |

| **Number of subjects in period 1** | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg | Part A: SAD: ALN-AAT 6.0 mg/kg |
|---|---|---|---|
| Started | 3 | 3 | 3 |
| Completed | 3 | 2 | 1 |
| Not completed | 0 | 1 | 2 |
| Reason not specified | - | - | 1 |
| Lost to follow-up | - | - | - |
| Withdrawal by subject | - | 1 | 1 |

| **Number of subjects in period 1** | Part B: MAD: Placebo | Part B: MAD: ALN-AAT 1.0 mg/kg |
|---|---|---|
| Started | 2 | 4 |
| Completed | 2 | 3 |
| Not completed | 0 | 1 |
| Reason not specified | - | - |
| Lost to follow-up | - | 1 |
| Withdrawal by subject | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Part A: SAD: Placebo |
| Reporting group description: | |
| A single dose of matching placebo was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 0.1 mg/kg |
| Reporting group description: | |
| A single dose of 0.1 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 0.3 mg/kg |
| Reporting group description: | |
| A single dose of 0.3 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 1.0 mg/kg |
| Reporting group description: | |
| A single dose of 1.0 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 3.0 mg/kg |
| Reporting group description: | |
| A single dose of 3.0 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 6.0 mg/kg |
| Reporting group description: | |
| A single dose of 6.0 mg/kg ALN-AAT was administered. | |

| | |
|---|---|
| Reporting group title | Part B: MAD: Placebo |
| Reporting group description: | |
| Multiple doses (once every 4 weeks) of matching placebo were administered. | |
| Reporting group title | Part B: MAD: ALN-AAT 1.0 mg/kg |
| Reporting group description: | |
| Multiple doses (once every 4 weeks) of 1.0 mg/kg ALN-AAT were administered. | |

| Reporting group values | Part A: SAD: Placebo | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg |
|---|---|---|---|
| Number of subjects | 5 | 3 | 3 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 30 | 29 | 31 |
| standard deviation | ± 10.3 | ± 9.8 | ± 13.3 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 0 | 1 |
| Male | 2 | 3 | 2 |

| Reporting group values | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg | Part A: SAD: ALN-AAT 6.0 mg/kg |
|---|---|---|---|
| Number of subjects | 3 | 3 | 3 |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 45 | 44 | 30 |
| standard deviation | ± 18.2 | ± 14.9 | ± 7.0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 1 | 2 | 2 |
| Male | 2 | 1 | 1 |

| **Reporting group values** | Part B: MAD: Placebo | Part B: MAD: ALN-AAT 1.0 mg/kg | Total |
|---|---|---|---|
| Number of subjects | 2 | 4 | 26 |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 28 | 32 | |
| standard deviation | ± 5.7 | ± 16.5 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 2 | 13 |
| Male | 0 | 2 | 13 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Part A: SAD: Placebo |
| Reporting group description: | |
| A single dose of matching placebo was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 0.1 mg/kg |
| Reporting group description: | |
| A single dose of 0.1 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 0.3 mg/kg |
| Reporting group description: | |
| A single dose of 0.3 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 1.0 mg/kg |
| Reporting group description: | |
| A single dose of 1.0 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 3.0 mg/kg |
| Reporting group description: | |
| A single dose of 3.0 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 6.0 mg/kg |
| Reporting group description: | |
| A single dose of 6.0 mg/kg ALN-AAT was administered. | |

| | |
|---|---|
| Reporting group title | Part B: MAD: Placebo |
| Reporting group description: | |
| Multiple doses (once every 4 weeks) of matching placebo were administered. | |
| Reporting group title | Part B: MAD: ALN-AAT 1.0 mg/kg |
| Reporting group description: | |
| Multiple doses (once every 4 weeks) of 1.0 mg/kg ALN-AAT were administered. | |

### Primary: Percentage of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs Leading to Study Discontinuation

| | |
|---|---|
| End point title | Percentage of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs Leading to Study Discontinuation[1] |
| End point description: | |
| An AE is any untoward medical occurrence in a clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An SAE is any untoward medical occurrence that at any dose of study drug: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly or birth defect. Safety population included all subjects who received at least 1 dose of study drug (ALN-AAT or placebo). | |
| End point type | Primary |
| End point timeframe: | |
| Part A: up to 160 days plus up to 24 months follow-up; Part B: up to 244 days plus up to 24 months follow-up | |

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: Only descriptive data were planned to be reported for this Safety endpoint.

| End point values | Part A: SAD: Placebo | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 3 | 3 | 3 |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Adverse Events (AEs) | 100 | 100 | 100 | 66.7 |
| Serious Adverse Events (SAEs) | 0 | 0 | 0 | 0 |
| AEs Leading to Study Discontinuation | 0 | 0 | 0 | 0 |

| End point values | Part A: SAD: ALN-AAT 3.0 mg/kg | Part A: SAD: ALN-AAT 6.0 mg/kg | Part B: MAD: Placebo | Part B: MAD: ALN-AAT 1.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 2 | 4 |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Adverse Events (AEs) | 100 | 100 | 100 | 100 |
| Serious Adverse Events (SAEs) | 0 | 0 | 0 | 0 |
| AEs Leading to Study Discontinuation | 0 | 0 | 0 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Concentration (Cmax) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

| End point title | Maximum Concentration (Cmax) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A[2] |
|---|---|

End point description:

Pharmacokinetic (PK) population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Day 0: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| End point values | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: nanogram (ng)/millilitre (mL) | | | | |
| arithmetic mean (standard deviation) | 24.4 (± 7.52) | 50.4 (± 11.9) | 167 (± 56.2) | 464 (± 48.6) |

| End point values | Part A: SAD: ALN-AAT 6.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: nanogram (ng)/millilitre (mL) | | | | |
| arithmetic mean (standard deviation) | 1270 (± 387) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Concentration (Cmax) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

| End point title | Maximum Concentration (Cmax) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B[3] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Days 0 and 84: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Pharmacokinetic (PK) endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| End point values | Part B: MAD: ALN-AAT 1.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 0 | 179 (± 38.4) | | | |
| Day 84 | 133 (± 22.5) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Cmax (tmax) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

| End point title | Time to Cmax (tmax) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A[4] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Day 0: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 1.00 (0.50 to 4.00) | 4.00 (0.50 to 4.00) | 4.00 (4.00 to 4.00) | 6.03 (0.50 to 12.00) |

| **End point values** | Part A: SAD: ALN-AAT 6.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 0.50 (0.50 to 4.00) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Cmax (tmax) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

| End point title | Time to Cmax (tmax) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B[5] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Days 0 and 84: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| End point values | Part B: MAD: ALN-AAT 1.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Day 0 | 4.00 (4.00 to 4.00) | | | |
| Day 84 | 4.00 (4.00 to 6.00) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUC0-last) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

| End point title | Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUC0-last) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A[6] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Day 0: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| End point values | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 127 (± 26.3) | 352 (± 41.4) | 2130 (± 106) | 9260 (± 2770) |

| End point values | Part A: SAD: ALN-AAT 6.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 17400 (± 4840) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUC0-τ) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

| End point title | Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUC0-τ) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B[7] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Days 0 and 84: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part B: MAD: ALN-AAT 1.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 0 | 1470 (± 183) | | | |
| Day 84 | 1280 (± 262) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Terminal Half-life (t1/2) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

| End point title | Terminal Half-life (t1/2) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A[8] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data. Here, 9999= not calculated.

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

End point timeframe:

Day 0: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 9999 (± 9999) | 4.18 (± 1.32) | 8.83 (± 2.75) | 6.15 (± 1.01) |

| **End point values** | Part A: SAD: ALN-AAT 6.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 6.96 (± 0.436) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Terminal Half-life (t1/2) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

| End point title | Terminal Half-life (t1/2) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B[9] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data. Here, 9999= not calculated.

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

End point timeframe:

Days 0 and 84: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part B: MAD: ALN-AAT 1.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 0 | 3.59 (± 9999) | | | |
| Day 84 | 9999 (± 9999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent Systemic Clearance (CL/F) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

| End point title | Apparent Systemic Clearance (CL/F) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A[10] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data. Here, 9999= not calculated.

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

End point timeframe:

Day 0: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: Litre (L)/ hr | | | | |
| arithmetic mean (standard deviation) | 9999 (± 9999) | 43.6 (± 0.000237) | 31.6 (± 5.00) | 22.5 (± 7.74) |

| **End point values** | Part A: SAD: ALN-AAT 6.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Litre (L)/ hr | | | | |
| arithmetic mean (standard deviation) | 21.9 (± 1.14) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent Systemic Clearance (CL/F) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

| End point title | Apparent Systemic Clearance (CL/F) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B[11] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data. Here, 9999= not calculated.

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

End point timeframe:

Days 0 and 84: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part B: MAD: ALN-AAT 1.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: L/hr | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 0 | 39.1 (± 9999) | | | |
| Day 84 | 9999 (± 9999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent Volume of Distribution (Vz/F) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

| End point title | Apparent Volume of Distribution (Vz/F) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A[12] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data. Here, 9999= not calculated.

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

End point timeframe:

Day 0: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: Litre (L) | | | | |
| arithmetic mean (standard deviation) | 9999 (± 9999) | 263 (± 83.1) | 393 (± 61.8) | 194 (± 36.1) |

| End point values | Part A: SAD: ALN-AAT 6.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Litre (L) | | | | |
| arithmetic mean (standard deviation) | 220 (± 18.0) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent Volume of Distribution (Vz/F) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

| End point title | Apparent Volume of Distribution (Vz/F) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B[13] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data. Here, 9999=not calculated.

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

End point timeframe:

Days 0 and 84: predose, 0.5 hour (hr), 1, 2, 4, 6, 8, 12, 24, 48 hr

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| End point values | Part B: MAD: ALN-AAT 1.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: Litre (L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 0 | 203 (± 9999) | | | |
| Day 84 | 9999 (± 9999) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Fraction Excreted in Urine (fe) of ALN-AAT After Single Ascending Dose (SAD) Part A

| End point title | Fraction Excreted in Urine (fe) of ALN-AAT After Single Ascending Dose (SAD) Part A[14] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Day 0: predose, 0-6 hr, 6-12 hr, 12-24 hr, 48 hr

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| **End point values** | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 12.7 (± 4.50) | 11.3 (± 1.36) | 16.0 (± 0.964) | 13.4 (± 2.07) |

| **End point values** | Part A: SAD: ALN-AAT 6.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 12.1 (± 7.38) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Fraction Excreted in Urine (fe) of ALN-AAT After Multiple Ascending Dose (MAD) Part B

| End point title | Fraction Excreted in Urine (fe) of ALN-AAT After Multiple Ascending Dose (MAD) Part B[15] |
|---|---|

End point description:

PK population included all subjects who received at least 1 dose of ALN AAT, had at least 1 post-dose PK parameter and who have evaluable PK data.

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

End point timeframe:

Days 0 and 84: predose, 0-6 hr, 6-12 hr, 12-24 hr and 48 hr

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK endpoints are reported only for arms, which received ALN-AAT (not placebo). Part A and B arms are reported separately as PK data were collected at different days during the study.

| End point values | Part B: MAD: ALN-AAT 1.0 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 0 | 13.3 (± 3.57) | | | |
| Day 84 | 11.6 (± 5.88) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Serum Alpha-1 Antitrypsin (AAT) Levels After Single Ascending Dose (SAD) Part A

| End point title | Change from Baseline in Serum Alpha-1 Antitrypsin (AAT) Levels After Single Ascending Dose (SAD) Part A[16] |
|---|---|

End point description:

Serum AAT levels were analysed using a validated enzyme-linked immunosorbent assay (ELISA). AAT follow-up monitoring was repeated every 28 days. The reporting arms 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 6.0 mg/kg had 3, 8, 9, 20 and 28 follow-up monitoring visits respectively. Pharmacodynamic (PD) analysis set included all subjects who received at least 1 dose of study drug (ALN AAT or placebo) and had at least 1 post-dose serum AAT. Number of subjects analysed as indicated except: 0.1 mg/kg Follow-up Monitoring 1-3: n=2; 0.3 mg/kg Follow-up Monitoring 1-8: n=2; 1.0 mg/kg Follow-up Monitoring 4-8: n=2 and Follow-up Monitoring 9: n=1; 3.0 mg/kg Follow-up Monitoring 8-9: n=2 and Follow-up Monitoring 10-20: n=1; 6.0 mg/kg Follow-up Monitoring 4-7: n=2 and Follow-up Monitoring 8-28: n=1. 9999= no subject was analysed for follow-up monitoring and 99999= not calculated.

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

End point timeframe:

Baseline, Days 1, 2, 7, 14, 21, 28, 35, 42, 56, 70, Follow up monitoring visit (every 28 days) up to 28 follow-up monitoring visits (approximately 784 days)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Part A and B arms are reported separately as ATT data were collected at a different number of monitoring time points during follow-up.

| End point values | Part A: SAD: Placebo | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg | Part A: SAD: ALN-AAT 1.0 mg/kg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 3 | 3 | 3 |
| Units: microgram (ug)/ mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 1501.32 (± 292.554) | 1072.59 (± 123.304) | 1398.14 (± 89.754) | 1324.76 (± 62.951) |
| Day 1 | -63.98 (± 233.611) | 23.93 (± 97.432) | 161.13 (± 247.049) | -156.16 (± 114.833) |
| Day 2 | -182.74 (± 282.496) | 55.54 (± 105.483) | -75.98 (± 227.814) | 42.79 (± 190.179) |
| Day 7 | 251.19 (± 433.017) | 140.75 (± 97.611) | -65.79 (± 153.112) | -386.43 (± 53.904) |

| | | | | |
|---|---|---|---|---|
| Day 14 | -259.52 (± 151.892) | -77.26 (± 141.127) | -293.68 (± 167.243) | -547.89 (± 170.703) |
| Day 21 | 24.99 (± 277.963) | -132.79 (± 194.798) | -408.23 (± 141.121) | -555.81 (± 236.204) |
| Day 28 | 44.80 (± 252.060) | -214.92 (± 192.059) | -324.93 (± 102.329) | -656.53 (± 161.615) |
| Day 35 | 46.04 (± 217.424) | -271.23 (± 44.454) | -422.28 (± 303.545) | -695.15 (± 226.029) |
| Day 42 | 95.11 (± 192.039) | -253.40 (± 172.277) | -585.86 (± 135.380) | -664.63 (± 242.678) |
| Day 56 | -76.71 (± 205.776) | -429.37 (± 197.559) | -618.68 (± 173.650) | -680.77 (± 133.329) |
| Day 70 | -16.72 (± 289.306) | -421.91 (± 105.216) | -553.01 (± 167.934) | -648.87 (± 154.921) |
| Follow-Up AAT Monitoring 1 | 9999 (± 9999) | -226.15 (± 65.360) | -582.75 (± 52.849) | -548.90 (± 228.785) |
| Follow-Up AAT Monitoring 2 | 9999 (± 9999) | -224.83 (± 190.612) | -299.97 (± 125.292) | -368.34 (± 179.988) |
| Follow-Up AAT Monitoring 3 | 9999 (± 9999) | -117.53 (± 392.902) | -610.65 (± 61.462) | -457.28 (± 414.259) |
| Follow-Up AAT Monitoring 4 | 9999 (± 9999) | 9999 (± 9999) | -431.58 (± 237.319) | -460.93 (± 7.590) |
| Follow-Up AAT Monitoring 5 | 9999 (± 9999) | 9999 (± 9999) | -648.64 (± 206.001) | -458.80 (± 61.924) |
| Follow-Up AAT Monitoring 6 | 9999 (± 9999) | 9999 (± 9999) | -277.67 (± 119.020) | -460.13 (± 64.738) |
| Follow-Up AAT Monitoring 7 | 9999 (± 9999) | 9999 (± 9999) | -357.66 (± 118.299) | -271.00 (± 10.192) |
| Follow-Up AAT Monitoring 8 | 9999 (± 9999) | 9999 (± 9999) | -39.29 (± 169.720) | -128.01 (± 112.305) |
| Follow-Up AAT Monitoring 9 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | -34.42 (± 99999) |
| Follow-Up AAT Monitoring 10 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 11 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 12 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 13 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 14 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 15 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 16 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 17 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 18 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 19 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 20 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 21 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 22 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 23 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 24 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 25 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 26 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 27 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |
| Follow-Up AAT Monitoring 28 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |

| **End point values** | Part A: SAD: ALN-AAT 3.0 mg/kg | Part A: SAD: ALN-AAT 6.0 mg/kg | | |
|---|---|---|---|---|

| Subject group type | Reporting group | Reporting group | | |
|---|---|---|---|---|
| Number of subjects analysed | 3 | 3 | | |
| Units: microgram (ug)/ mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 1652.31 (± 224.862) | 1687.27 (± 604.319) | | |
| Day 1 | -23.60 (± 277.341) | -118.88 (± 370.215) | | |
| Day 2 | 68.90 (± 653.373) | -190.57 (± 331.197) | | |
| Day 7 | -279.27 (± 465.294) | 181.10 (± 629.055) | | |
| Day 14 | -791.47 (± 191.362) | -951.52 (± 586.210) | | |
| Day 21 | -954.19 (± 249.016) | -1228.73 (± 592.668) | | |
| Day 28 | -1099.55 (± 263.405) | -1321.59 (± 594.704) | | |
| Day 35 | -1115.95 (± 214.412) | -1356.90 (± 637.242) | | |
| Day 42 | -1132.63 (± 130.877) | -1381.10 (± 576.775) | | |
| Day 56 | -1256.09 (± 139.961) | -1402.55 (± 568.159) | | |
| Day 70 | -1168.36 (± 215.997) | -1402.43 (± 571.959) | | |
| Follow-Up AAT Monitoring 1 | -1105.29 (± 210.020) | -1327.43 (± 584.095) | | |
| Follow-Up AAT Monitoring 2 | -1051.38 (± 342.808) | -1404.94 (± 603.714) | | |
| Follow-Up AAT Monitoring 3 | -988.21 (± 127.026) | -1380.31 (± 579.965) | | |
| Follow-Up AAT Monitoring 4 | -939.66 (± 381.668) | -1028.50 (± 282.600) | | |
| Follow-Up AAT Monitoring 5 | -921.68 (± 333.010) | -1001.55 (± 289.515) | | |
| Follow-Up AAT Monitoring 6 | -735.26 (± 564.615) | -907.90 (± 171.026) | | |
| Follow-Up AAT Monitoring 7 | -825.95 (± 298.470) | -896.96 (± 215.729) | | |
| Follow-Up AAT Monitoring 8 | -514.41 (± 751.798) | -609.15 (± 99999) | | |
| Follow-Up AAT Monitoring 9 | -516.16 (± 537.665) | -524.23 (± 99999) | | |
| Follow-Up AAT Monitoring 10 | -892.07 (± 99999) | -554.68 (± 99999) | | |
| Follow-Up AAT Monitoring 11 | -873.49 (± 99999) | -663.54 (± 99999) | | |
| Follow-Up AAT Monitoring 12 | -776.81 (± 99999) | -560.19 (± 99999) | | |
| Follow-Up AAT Monitoring 13 | -403.93 (± 99999) | -307.12 (± 99999) | | |
| Follow-Up AAT Monitoring 14 | -683.10 (± 99999) | -551.76 (± 99999) | | |
| Follow-Up AAT Monitoring 15 | -787.45 (± 99999) | -465.69 (± 99999) | | |
| Follow-Up AAT Monitoring 16 | -619.24 (± 99999) | -468.27 (± 99999) | | |
| Follow-Up AAT Monitoring 17 | -100.74 (± 99999) | -437.77 (± 99999) | | |

| | | | | |
|---|---|---|---|---|
| Follow-Up AAT Monitoring 18 | -448.64 (± 99999) | -312.95 (± 99999) | | |
| Follow-Up AAT Monitoring 19 | -257.20 (± 99999) | -252.67 (± 99999) | | |
| Follow-Up AAT Monitoring 20 | -514.99 (± 99999) | -345.95 (± 99999) | | |
| Follow-Up AAT Monitoring 21 | 9999 (± 9999) | -103.09 (± 99999) | | |
| Follow-Up AAT Monitoring 22 | 9999 (± 9999) | -32.48 (± 99999) | | |
| Follow-Up AAT Monitoring 23 | 9999 (± 9999) | -191.16 (± 99999) | | |
| Follow-Up AAT Monitoring 24 | 9999 (± 9999) | -95.06 (± 99999) | | |
| Follow-Up AAT Monitoring 25 | 9999 (± 9999) | 11.06 (± 99999) | | |
| Follow-Up AAT Monitoring 26 | 9999 (± 9999) | -58.99 (± 99999) | | |
| Follow-Up AAT Monitoring 27 | 9999 (± 9999) | -156.06 (± 99999) | | |
| Follow-Up AAT Monitoring 28 | 9999 (± 9999) | 907.87 (± 99999) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Serum Alpha-1 Antitrypsin (AAT) Levels After Multiple Ascending Dose (MAD) Part B

| End point title | Change from Baseline in Serum Alpha-1 Antitrypsin (AAT) Levels After Multiple Ascending Dose (MAD) Part B[17] |
|---|---|

End point description:

Serum AAT levels were analysed using a validated ELISA. AAT follow-up monitoring was repeated every 28 days. The reporting arm 1.0 mg/kg had 19 follow-up monitoring visits. PD analysis set included all subjects who received at least 1 dose of study drug (ALN AAT or placebo) and had at least 1 post-dose serum AAT. Number of subjects analysed as indicated except: 1.0 mg/kg Follow-up Monitoring 6: n=3, Follow-up Monitoring 12-18: n=2 and Follow-up Monitoring 19: n=1. 9999= no subject was analysed for follow-up monitoring and 99999= not calculated.

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

End point timeframe:

Baseline, Days 1, 7, 14, 21, 28, 42, 56, 70, 84, 98, 105, 112, 126, 140, 154 Follow up monitoring visit (every 28 days) up to 19 follow-up monitoring visits (approximately 532 days)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Part A and B arms are reported separately as ATT data were collected at a different number of monitoring time points during follow-up.

| End point values | Part B: MAD: Placebo | Part B: MAD: ALN-AAT 1.0 mg/kg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 4 | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|---|---|---|---|
| Baseline | 1521.44 (± 320.595) | 1630.96 (± 288.691) | | |
| Day 1 | -183.78 (± 29.147) | -85.44 (± 197.651) | | |
| Day 7 | -36.60 (± 246.625) | -349.78 (± 120.151) | | |
| Day 14 | -193.70 (± 228.254) | -555.10 (± 310.907) | | |
| Day 21 | -394.05 (± 118.377) | -832.45 (± 303.653) | | |
| Day 28 | -147.97 (± 29.020) | -841.91 (± 246.344) | | |
| Day 42 | -144.50 (± 123.730) | -1113.25 (± 227.318) | | |
| Day 56 | -59.15 (± 16.681) | -1215.76 (± 272.928) | | |
| Day 70 | -201.72 (± 31.855) | -1210.26 (± 278.535) | | |
| Day 84 | 27.89 (± 74.154) | -1330.08 (± 212.621) | | |
| Day 98 | 12.27 (± 543.687) | -1277.70 (± 211.994) | | |
| Day 105 | -18.10 (± 66.772) | -1352.05 (± 188.138) | | |
| Day 112 | -111.76 (± 241.604) | -1346.01 (± 208.292) | | |
| Day 126 | -384.62 (± 145.310) | -1306.78 (± 145.804) | | |
| Day 140 | -158.22 (± 57.573) | -1327.03 (± 192.588) | | |
| Day 154 | -235.20 (± 7.764) | -1268.20 (± 202.673) | | |
| Follow-Up AAT Monitoring 1 | 9999 (± 9999) | -1225.79 (± 228.573) | | |
| Follow-Up AAT Monitoring 2 | 9999 (± 9999) | -1209.57 (± 277.196) | | |
| Follow-Up AAT Monitoring 3 | 9999 (± 9999) | -1132.19 (± 368.900) | | |
| Follow-Up AAT Monitoring 4 | 9999 (± 9999) | -1100.38 (± 409.101) | | |
| Follow-Up AAT Monitoring 5 | 9999 (± 9999) | -1065.72 (± 487.221) | | |
| Follow-Up AAT Monitoring 6 | 9999 (± 9999) | -794.32 (± 400.770) | | |
| Follow-Up AAT Monitoring 7 | 9999 (± 9999) | -961.89 (± 491.672) | | |
| Follow-Up AAT Monitoring 8 | 9999 (± 9999) | -829.66 (± 587.410) | | |
| Follow-Up AAT Monitoring 9 | 9999 (± 9999) | -782.48 (± 494.649) | | |
| Follow-Up AAT Monitoring 10 | 9999 (± 9999) | -679.66 (± 448.771) | | |
| Follow-Up AAT Monitoring 11 | 9999 (± 9999) | -607.71 (± 461.639) | | |
| Follow-Up AAT Monitoring 12 | 9999 (± 9999) | -1055.14 (± 214.713) | | |
| Follow-Up AAT Monitoring 13 | 9999 (± 9999) | -1147.27 (± 277.179) | | |
| Follow-Up AAT Monitoring 14 | 9999 (± 9999) | -1118.70 (± 311.438) | | |
| Follow-Up AAT Monitoring 15 | 9999 (± 9999) | -1041.33 (± 250.761) | | |

| | | | | |
|---|---|---|---|---|
| Follow-Up AAT Monitoring 16 | 9999 (± 9999) | -956.44 (± 372.872) | | |
| Follow-Up AAT Monitoring 17 | 9999 (± 9999) | -903.09 (± 169.317) | | |
| Follow-Up AAT Monitoring 18 | 9999 (± 9999) | -738.61 (± 406.417) | | |
| Follow-Up AAT Monitoring 19 | 9999 (± 9999) | -630.47 (± 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Part A: up to 160 days plus up to 24 months follow-up; Part B: up to 244 days plus up to 24 months follow-up | |
| Adverse event reporting additional description: | |
| Safety population included all subjects who received at least 1 dose of study drug (ALN-AAT or placebo). | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Part A: SAD: Placebo |
| Reporting group description: | |
| A single dose of matching placebo was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 0.1 mg/kg |
| Reporting group description: | |
| A single dose of 0.1 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 0.3 mg/kg |
| Reporting group description: | |
| A single dose of 0.3 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 1.0 mg/kg |
| Reporting group description: | |
| A single dose of 1.0 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 3.0 mg/kg |
| Reporting group description: | |
| A single dose of 3.0 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part A: SAD: ALN-AAT 6.0 mg/kg |
| Reporting group description: | |
| A single dose of 6.0 mg/kg ALN-AAT was administered. | |
| Reporting group title | Part B: MAD: Placebo |
| Reporting group description: | |
| Multiple dosed (once every 4 weeks) of matching placebo were administered. | |
| Reporting group title | Part B: MAD: ALN-AAT 1.0 mg/kg |
| Reporting group description: | |
| Multiple doses (once every 4 weeks) of 1.0 mg/kg ALN-AAT were administered. | |

| Serious adverse events | Part A: SAD: Placebo | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg | Part A: SAD: ALN-AAT 6.0 mg/kg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Part B: MAD: Placebo | Part B: MAD: ALN-AAT 1.0 mg/kg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | Part A: SAD: Placebo | Part A: SAD: ALN-AAT 0.1 mg/kg | Part A: SAD: ALN-AAT 0.3 mg/kg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 5 (100.00%) | 3 / 3 (100.00%) | 3 / 3 (100.00%) |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Injection site dysaesthesia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site bruising | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |

| | | | |
|---|---|---|---|
| Allergy to animal | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Burns first degree | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Head injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Pinguecula | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Toothache | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Bladder irritation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 3 (66.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 2 | 1 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Part A: SAD: ALN-AAT 1.0 mg/kg | Part A: SAD: ALN-AAT 3.0 mg/kg | Part A: SAD: ALN-AAT 6.0 mg/kg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 3 / 3 (100.00%) | 3 / 3 (100.00%) |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site dysaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Injection site bruising | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Injection site pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Allergy to animal | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Burns first degree | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 3 (66.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Eye disorders | | | |
| Pinguecula | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psoriasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Bladder irritation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 1 | 1 | 2 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Herpes simplex | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Part B: MAD: Placebo | Part B: MAD: ALN-AAT 1.0 mg/kg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 4 / 4 (100.00%) | |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Injection site dysaesthesia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injection site bruising | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Injection site pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Immune system disorders | | | |
| Allergy to animal | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Burns first degree | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 1 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|---|---|---|---|
| Sensory disturbance<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Eye disorders<br>Pinguecula<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Toothache<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 | |
| Umbilical hernia<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 1 / 2 (50.00%)<br>1 | 0 / 4 (0.00%)<br>0 | |
| Nausea<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | |
| Cheilitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Rash | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Bladder irritation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 2 / 4 (50.00%) | |
| occurrences (all) | 1 | 2 | |

| | | | |
|---|---|---|---|
| Fungal infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 February 2017 | Amended primarily to revise the study follow-up period, with the objective of potentially reducing the total burden of study follow up for some study subjects while ensuring patient safety. Subjects must continue in follow up until the blood AAT level has reached 80 percent of pre-treatment values OR has reached the lower limit of the normal range. |
| 18 December 2017 | The purpose of Protocol Amendment 2 to ALN-AAT-001 is to permit a final evaluation of the one remaining subject participating in this study. Amended so that subjects are required to be followed until one of the following criteria are met:<br>1. AAT levels return to at least 80% of the subject's mean pre treatment baseline, or<br>2. AAT levels return to the lower limit of the normal range, or<br>3. The subject has been followed for 24 months following administration of the last dose of study drug and blood AAT levels exceed 0.49 g/dL. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 03 January 2018 | Dosing of study subjects was suspended in February 2016, and subjects who had been dosed were followed per protocol until their AAT levels returned to normal, at which point the study was terminated. The study was terminated because of the observation of low incidence of asymptomatic, transiently elevated liver enzymes in a subset of study subjects. | - |

Notes:

### Limitations and caveats

None reported