



## 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
<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Number of subjects in period 1</b>	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	-	-	-

<b>Number of subjects in period 1</b>	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

<b>Number of subjects in period 1</b>	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 Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	30 ± 10.3	29 ± 9.8	31 ± 13.3
Gender categorical 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 Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	45 ± 18.2	44 ± 14.9	30 ± 7.0
Gender categorical Units: Subjects			
Female	1	2	2
Male	2	1	1

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

Age continuous Units: years arithmetic mean standard deviation	28 ± 5.7	32 ± 16.5	-
Gender categorical 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 <sup>[1]</sup>
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 (C<sub>max</sub>) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

End point title	Maximum Concentration (C <sub>max</sub> ) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A <sup>[2]</sup>
-----------------	--

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)

<b>End point values</b>	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 (C<sub>max</sub>) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

End point title	Maximum Concentration (C <sub>max</sub> ) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B <sup>[3]</sup>
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.

<b>End point values</b>	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 C<sub>max</sub> (t<sub>max</sub>) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

End point title	Time to C <sub>max</sub> (t <sub>max</sub> ) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A <sup>[4]</sup>
-----------------	---

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 <sup>[5]</sup>
-----------------	--

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.

<b>End point values</b>	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 (AUC<sub>0-last</sub>) 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 (AUC <sub>0-last</sub> ) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A <sup>[6]</sup>
-----------------	--

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.

<b>End point values</b>	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)

<b>End point values</b>	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 (AUC<sub>0-τ</sub>) 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 (AUC <sub>0-τ</sub> ) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B <sup>[7]</sup>
-----------------	---

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 (t<sub>1/2</sub>) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

End point title	Terminal Half-life (t <sub>1/2</sub> ) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A <sup>[8]</sup>
-----------------	---

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 (t<sub>1/2</sub>) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

End point title	Terminal Half-life (t <sub>1/2</sub> ) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B <sup>[9]</sup>
-----------------	---

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 <sup>[10]</sup>
-----------------	--

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 <sup>[11]</sup>
-----------------	--

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.

<b>End point values</b>	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 (V<sub>z</sub>/F) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A

End point title	Apparent Volume of Distribution (V <sub>z</sub> /F) of ALN-AAT in Plasma After Single Ascending Dose (SAD) Part A <sup>[12]</sup>
-----------------	---

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.

<b>End point values</b>	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)

<b>End point values</b>	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 (V<sub>z</sub>/F) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B

End point title	Apparent Volume of Distribution (V <sub>z</sub> /F) of ALN-AAT in Plasma After Multiple Ascending Dose (MAD) Part B <sup>[13]</sup>
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.

<b>End point values</b>	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 <sup>[14]</sup>
-----------------	---

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 <sup>[15]</sup>
-----------------	---

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.

<b>End point values</b>	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 <sup>[16]</sup>
-----------------	---

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.

<b>End point values</b>	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)

<b>End point values</b>	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 <sup>[17]</sup>
-----------------	---

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

<b>Serious adverse events</b>	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

<b>Serious adverse events</b>	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 %

<b>Non-serious adverse events</b>	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 occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Respiratory, thoracic and mediastinal disorders			
Productive cough subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Nasal congestion subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Psychiatric disorders			
Depressed mood subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0

Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Injury, poisoning and procedural complications			
Burns first degree subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Head injury subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Ligament sprain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Muscle rupture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Muscle strain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Migraine subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Sensory disturbance subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Eye disorders			
Pinguecula subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 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 occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Renal and urinary disorders Bladder irritation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Neck pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Tendonitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 3 (66.67%) 2	1 / 3 (33.33%) 1
Fungal infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Herpes simplex subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 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

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

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

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



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

Rash pruritic subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 4 (0.00%) 0	
Psoriasis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 4 (25.00%) 1	
Rash subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 4 (25.00%) 1	
Renal and urinary disorders Bladder irritation subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 4 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 4 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 4 (0.00%) 0	
Neck pain subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 4 (0.00%) 0	
Tendonitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 4 (0.00%) 0	
Arthralgia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 4 (25.00%) 1	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 4 (25.00%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	2 / 4 (50.00%) 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: 1. AAT levels return to at least 80% of the subject's mean pre treatment baseline, or 2. AAT levels return to the lower limit of the normal range, or 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