Clinical trial results:
A Pilot Open Label, Multi-dose, Phase 2 Study to Assess the Safety and Efficacy of Fazirsiran (TAK-999, ARO-AAT) in Patients with Alpha-1 Antitrypsin Deficiency Associated Liver Disease (AATD)

Summary

EudraCT number	2019-000068-86
Trial protocol	GB DE AT
Global end of trial date	14 December 2023

Results information

Result version number	v1 (current)
This version publication date	29 December 2024
First version publication date	29 December 2024

Trial information

Trial identification

Sponsor protocol code	AROAAT2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03946449
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Arrowhead Pharmaceuticals, Inc.
Sponsor organisation address	177 East Colorado Boulevard, Suite 700, Pasadena, CA, United States, 91105
Public contact	Mei Ling Chang-Lok, Arrowhead Pharmaceuticals, Inc., 001 6263043400, mchanglok@arrowheadpharma.com
Scientific contact	Chief Operating Officer, Arrowhead Pharmaceuticals, Inc., 001 6263043400, info@arrowheadpharma.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	14 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate change from baseline over time in total, soluble, and insoluble Z-AAT concentrations in the liver of patients with AAT-associated liver disease.

Protection of trial subjects:

All eligible participants had the study explained by the PI or designee. They received a full explanation, in lay terms, of the aims of the study, the discomforts, risks and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It was explained that the study is for research purposes only and was not expected to provide any therapeutic benefit to the individual. It was pointed out that they could withdraw from the study at any time without prejudice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	16
EEA total number of subjects	14

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)	14

From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All eligible subjects required a pre-dose biopsy completed as part of the study within the screening window. Participants consisted of male and female adult homozygous Z allele individuals (PiZZ; based on genotype completed at Screening or from a source verifiable document) alpha-1 antitrypsin patients.

Period 1

Period 1 title	Primary Study Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ARO-AAT 100 mg Cohort 1b

Arm description:

Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Arm title	ARO-AAT 200 mg Cohort 1

Arm description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Arm title	ARO-AAT 200 mg Cohort 2

Arm description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods.

Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 17 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Number of subjects in period 1	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1	ARO-AAT 200 mg Cohort 2
Started	4	4	8
Completed	4	4	8

Period 2

Period 2 title	Treatment Extension I
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ARO-AAT 100 mg Cohort 1b

Arm description:

Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Arm title	ARO-AAT 200 mg Cohort 1

Arm description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses,

with 2 optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Arm title	ARO-AAT 200 mg Cohort 2

Arm description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 17 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Number of subjects in period 2[1]	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1	ARO-AAT 200 mg Cohort 2
Started	4	4	7
Completed	4	4	7

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One subject who completed the Primary Study Period did not continue to the Treatment Extension I.

Period 3

Period 3 title	Treatment Extension II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	ARO-AAT 100 mg Cohort 1b

Arm description:

Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W. As of global protocol version 7.0 (21-Jul-2022) / German protocol version 2.6 (29-Jul-2022) and after applicable regulatory, Ethics Committee and local approval, participants in cohort 1b switched from 100 mg to 200 mg while maintaining their dosing schedule.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Arm title	ARO-AAT 200 mg Cohort 1

Arm description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Arm title	ARO-AAT 200 mg Cohort 2

Arm description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 17 doses.

Arm type	Experimental
Investigational medicinal product name	ARO-AAT Injection
Investigational medicinal product code	
Other name	fazirsiran, TAK-999
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each dose of fazirsiran will be administered by subcutaneous injection.

Number of subjects in period 3	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1	ARO-AAT 200 mg Cohort 2
Started	4	4	7
Completed	4	4	4
Not completed	0	0	3
Rolled over to another study	-	-	2
Consent withdrawn by subject	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ARO-AAT 100 mg Cohort 1b
Reporting group description:	
Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods. Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W). Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W. The maximum number of doses for participants completing the treatment extension periods was 15 doses.	
Reporting group title	ARO-AAT 200 mg Cohort 1
Reporting group description:	
Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods. Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W). Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W. The maximum number of doses for participants completing the treatment extension periods was 15 doses.	
Reporting group title	ARO-AAT 200 mg Cohort 2
Reporting group description:	
Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods. Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W). Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W. The maximum number of doses for participants completing the treatment extension periods was 17 doses.	

Reporting group values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1	ARO-AAT 200 mg Cohort 2
Number of subjects	4	4	8
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.8	44.5	54.6
standard deviation	± 10.01	± 17.00	± 13.68
Gender categorical Units: Subjects			
Female	1	0	1
Male	3	4	7
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Non-Hispanic or Latino	4	4	8
Race Units: Subjects			
White	4	4	8
Insoluble ZAAT Units: nmol/g			
arithmetic mean	35.9750	33.2750	37.4500
standard deviation	± 16.51694	± 53.31019	± 27.73075

Partial ZAAT			
Units: nmol/g			
arithmetic mean	26.3500	24.3000	23.3125
standard deviation	± 5.18813	± 10.58899	± 7.59914
Total ZAAT			
Units: nmol/g			
arithmetic mean	62.3250	57.5750	60.7625
standard deviation	± 15.81210	± 59.65391	± 34.04199

Reporting group values	Total		
Number of subjects	16		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	2		
Male	14		
Ethnicity			
Units: Subjects			
Hispanic or Latino	0		
Non-Hispanic or Latino	16		
Race			
Units: Subjects			
White	16		
Insoluble ZAAT			
Units: nmol/g			
arithmetic mean			
standard deviation	-		
Partial ZAAT			
Units: nmol/g			
arithmetic mean			
standard deviation	-		
Total ZAAT			
Units: nmol/g			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	ARO-AAT 100 mg Cohort 1b

Reporting group description:

Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Reporting group title	ARO-AAT 200 mg Cohort 1

Reporting group description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Reporting group title	ARO-AAT 200 mg Cohort 2

Reporting group description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 17 doses.

Reporting group title	ARO-AAT 100 mg Cohort 1b

Reporting group description:

Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Reporting group title	ARO-AAT 200 mg Cohort 1

Reporting group description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Reporting group title	ARO-AAT 200 mg Cohort 2

Reporting group description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 17 doses.

Reporting group title	ARO-AAT 100 mg Cohort 1b

Reporting group description:

Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W. As of global protocol version 7.0 (21-Jul-2022) / German protocol version 2.6 (29-Jul-2022) and after applicable regulatory, Ethics Committee and local approval, participants in cohort 1b switched from 100 mg to 200 mg while maintaining their dosing schedule.
The maximum number of doses for participants completing the treatment extension periods was 15

doses.

Reporting group title	ARO-AAT 200 mg Cohort 1

Reporting group description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 15 doses.

Reporting group title	ARO-AAT 200 mg Cohort 2

Reporting group description:

Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods.
Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W).
Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W.
The maximum number of doses for participants completing the treatment extension periods was 17 doses.

Primary: Percent Change From Baseline in Total Liver Z-AAT, Insoluble Liver-ZAAT, and Partial (Soluble) Liver Z-AAT: Cohorts 1/1b

End point title	Percent Change From Baseline in Total Liver Z-AAT, Insoluble Liver-ZAAT, and Partial (Soluble) Liver Z-AAT: Cohorts 1/1b[1][2]

End point description:

Full Analysis Set: all participants who received at least one dose of study drug and had baseline and post-dose liver biopsy histology results available.

End point type	Primary

End point timeframe:

Baseline, Week 24

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: Statistics planned per protocol for this endpoint are presented in the data table.

[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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percent change				
arithmetic mean (standard deviation)				
Total Liver Z-AAT	-83.07 (± 5.830)	-79.84 (± 10.519)		
Insoluble Liver-ZAAT	-81.58 (± 6.947)	-12.91 (± 131.702)		
Partial (Soluble) Liver Z-AAT	-85.36 (± 4.835)	-88.18 (± 5.718)		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in Total Liver Z-AAT, Insoluble Liver-ZAAT, and Partial (Soluble) Liver Z-AAT: Cohort 2

End point title	Percent Change From Baseline in Total Liver Z-AAT, Insoluble Liver-ZAAT, and Partial (Soluble) Liver Z-AAT: Cohort 2[3][4]

End point description:

Full Analysis Set: all participants who received at least one dose of study drug and had baseline and post-dose liver biopsy histology results available.

End point type	Primary

End point timeframe:

Baseline, Week 48

Notes:

[3] - 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: Statistics planned per protocol for this endpoint are presented in the data table.

[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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent change				
arithmetic mean (standard deviation)				
Total Liver Z-AAT	-90.26 (± 9.029)			
Insoluble Liver-ZAAT	-84.83 (± 19.920)			
Partial (Soluble) Liver Z-AAT	-92.64 (± 7.482)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Serum Z-AAT: Cohorts 1/1b

End point title	Percent Change From Baseline in Serum Z-AAT: Cohorts 1/1b[5]

End point description:

Full Analysis Set: all participants who received at least one dose of study drug and had baseline and post-dose liver biopsy histology results available.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 16, 24

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percent change				
arithmetic mean (standard deviation)				
Week 2	-69.12 (± 12.381)	-77.28 (± 7.394)		
Week 4	-80.24 (± 8.880)	-88.07 (± 4.931)		
Week 6	-87.27 (± 6.140)	-91.79 (± 3.795)		
Week 16	-78.61 (± 9.186)	-83.08 (± 6.269)		
Week 24	-83.85 (± 5.426)	-89.47 (± 3.738)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Serum Z-AAT: Cohort 2

End point title	Percent Change From Baseline in Serum Z-AAT: Cohort 2[6]

End point description:

Full Analysis Set: all participants who received at least one dose of study drug and had baseline and post-dose liver biopsy histology results available.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 16, 22, 28, 34, 40, 48

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent change				
arithmetic mean (standard deviation)				
Week 2	-72.08 (± 8.645)			
Week 4	-82.22 (± 7.476)			
Week 6	-89.92 (± 4.024)			
Week 16	-85.76 (± 6.106)			
Week 22	-90.87 (± 4.246)			
Week 28	-85.06 (± 7.847)			
Week 34	-89.54 (± 5.434)			

Week 40	-84.12 (± 12.433)			
Week 48	-89.58 (± 5.419)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine Aminotransferase (ALT) Values Over Time: Cohorts 1/1b

End point title	Alanine Aminotransferase (ALT) Values Over Time: Cohorts 1/1b[7]

End point description:

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2, Week 2, Week 4, Week 4 (24-48h post dose), Week 6, Week 16, Week 16 (24/48h post dose), Week 24

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=4, 4	58.5 (± 41.36)	87.8 (± 30.42)		
Day 2 (24-48 hr post-dose); n=4, 4	58.5 (± 42.68)	88.3 (± 32.72)		
Week 2; n=4, 4	76.5 (± 55.24)	99.8 (± 53.89)		
Week 4; n=4, 4	62.3 (± 35.77)	106.5 (± 42.57)		
Week 4 (24-48 hr post-dose); n=4, 4	60.3 (± 33.97)	99.0 (± 38.58)		
Week 6; n=4, 4	49.8 (± 25.16)	77.0 (± 20.85)		
Week 16; n=3, 4	35.7 (± 8.50)	49.8 (± 5.25)		
Week 16 (24-48 hr post-dose); n=4, 3	31.5 (± 8.85)	42.7 (± 3.06)		
Week 24; n=4, 4	27.8 (± 9.29)	39.5 (± 3.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: ALT Values Over Time: Cohort 2

End point title	ALT Values Over Time: Cohort 2[8]

End point description:

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2, Week 2, Week 4, Week 4 (24-48h post dose), Week 6, Week 16, Week 16 (24/48h post dose), Week 22, Week 28, Week 34, Week 40, Week 48

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=8	62.1 (± 14.98)			
Day 2 (24-48 hr post-dose); n=8	58.6 (± 15.59)			
Week 2; n=7	61.9 (± 20.17)			
Week 4; n=8	55.3 (± 14.09)			
Week 4 (24-48 hr post-dose); n=8	53.0 (± 14.83)			
Week 6; n=7	54.9 (± 9.79)			
Week 16; n=8	39.6 (± 13.13)			
Week 16 (24-48 hr post-dose); n=8	37.5 (± 11.61)			
Week 22; n=8	41.0 (± 14.58)			
Week 28; n=7	36.7 (± 15.76)			
Week 34; n=8	39.4 (± 11.13)			
Week 40; n=8	33.4 (± 10.08)			
Week 48; n=6	34.5 (± 10.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gamma Glutamyl Transferase (GGT) Values Over Time: Cohorts 1/1b

End point title	Gamma Glutamyl Transferase (GGT) Values Over Time: Cohorts 1/1b[9]

End point description:

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2, Week 2, Week 4, Week 4 (24-48h post dose), Week 6, Week 16, Week 16 (24/48h post dose), Week 24

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=4, 4	70.8 (± 35.30)	244.8 (± 355.68)		
Day 2 (24-48 hr post-dose); n=4, 4	70.5 (± 39.07)	247.3 (± 358.01)		
Week 2; n=4, 4	66.0 (± 37.15)	210.8 (± 304.4)		
Week 4; n=4, 4	73.0 (± 43.37)	222.0 (± 334.85)		
Week 4 (24-48 hr post-dose); n=4, 4	70.0 (± 45.19)	210.3 (± 312.0)		
Week 6; n=4, 4	64.0 (± 35.62)	199.3 (± 292.28)		
Week 16; n=4, 4	48.0 (± 23.25)	135.3 (± 190.31)		
Week 16 (24-48 hr post-dose); n=4, 3	48.0 (± 22.38)	161.7 (± 212.17)		
Week 24; n=4, 4	52.3 (± 28.31)	112.0 (± 156.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: GGT Values Over Time: Cohort 2

End point title	GGT Values Over Time: Cohort 2[10]

End point description:

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2, Week 2, Week 4, Week 4 (24-48h post dose), Week 6, Week 16, Week 16 (24/48h post dose), Week 22, Week 28, Week 34, Week 40, Week 48

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=8	62.5 (± 31.09)			
Day 2 (24-48 hr post-dose); n=8	62.1 (± 33.21)			
Week 2; n=7	60.6 (± 33.14)			
Week 4; n=8	59.1 (± 49.82)			

Week 4 (24-48 hr post-dose); n=8	57.6 (± 46.91)			
Week 6; n=7	58.0 (± 36.21)			
Week 16; n=8	49.1 (± 36.84)			
Week 16 (24-48 hr post-dose); n=8	48.3 (± 38.68)			
Week 22; n=8	48.5 (± 34.85)			
Week 28; n=8	44.5 (± 34.62)			
Week 34; n=8	45.3 (± 31.37)			
Week 40; n=8	45.3 (± 38.20)			
Week 48; n=8	48.5 (± 45.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fibrosis-4 index (FIB4) Score Values Over Time: Cohorts 1/1b

End point title	Fibrosis-4 index (FIB4) Score Values Over Time: Cohorts

End point description:

The FIB 4 score evaluates the degree of fibrosis in patients suspected of or already diagnosed with hepatic fibrosis. FIB-4 is calculated as (Age (years) * aspartate aminotransferease) / (platelets * √(ALT)).
The result provided from the above equation is interpreted according to two cut off values:
FIB 4 <1.45 indicates absence of cirrhosis (with a negative predictive value of 90% for advanced fibrosis);
FIB 4 between 1.45 - 3.25 are deemed inconclusive;
FIB 4 >3.25 indicates cirrhosis (with a positive predictive value of 65% for advanced fibrosis).

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2 (24-48 hr post-dose), Week 2, Week 4, Week 4 (24-48 hr post-dose), Week 6, Week 16, Week 16 (24-48 hr post-dose), Week 24

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: numerical score				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=4, 4	1.425 (± 0.3613)	1.583 (± 0.9085)		
Day 2 (24-48 hr post-dose); n=4, 4	1.353 (± 0.2699)	1.618 (± 0.9668)		
Week 2; n=4, 4	1.580 (± 0.5806)	1.900 (± 1.3056)		
Week 4; n=4, 4	1.260 (± 0.3840)	1.750 (± 1.3273)		
Week 4 (24-48 hr post-dose); n=4, 4	1.333 (± 0.4194)	1.760 (± 1.3867)		

Week 6; n=4, 4	1.355 (± 0.4612)	2.013 (± 1.1073)		
Week 16; n=3, 4	1.257 (± 0.3326)	1.605 (± 1.221)		
Week 16 (24-48 hr post-dose); n=3, 3	1.227 (± 0.2230)	1.940 (± 1.6210)		
Week 24; n=4, 4	1.265 (± 0.3196)	1.688 (± 1.2563)		

Statistical analyses

No statistical analyses for this end point

Secondary: FIB4 Values Over Time: Cohort 2

End point title	FIB4 Values Over Time: Cohort 2[12]

End point description:

The FIB 4 score evaluates the degree of fibrosis in patients suspected of or already diagnosed with hepatic fibrosis. FIB-4 is calculated as (Age (years) * aspartate aminotransferease) / (platelets * √(ALT)).
The result provided from the above equation is interpreted according to two cut off values:
FIB 4 <1.45 indicates absence of cirrhosis (with a negative predictive value of 90% for advanced fibrosis);
FIB 4 between 1.45 - 3.25 are deemed inconclusive;
FIB 4 >3.25 indicates cirrhosis (with a positive predictive value of 65% for advanced fibrosis).

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2 (24-48 hr post-dose), Week 2, Week 4, Week 4 (24-48 hr post-dose), Week 6, Week 16, Week 16 (24-48 hr post-dose), Week 22, Week 28, Week 28 + 1 day, Week 34, Week 40, Week 48

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: numerical score				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=8	1.395 (± 0.6634)			
Day 2 (24-48 hr post-dose); n=8	1.543 (± 0.8209)			
Week 2; n=7	1.383 (± 0.6358)			
Week 4; n=8	1.420 (± 0.7054)			
Week 4 (24-48 hr post-dose); n=8	1.356 (± 0.6344)			
Week 6; n=7	1.367 (± 0.6419)			

Week 16; n=8	1.299 (± 0.5636)			
Week 16 (24-48 hr post-dose); n=8	1.271 (± 0.6521)			
Week 22; n=8	1.336 (± 0.6269)			
Week 28; n=7	1.377 (± 0.7152)			
Week 34; n=7	1.239 (± 0.7527)			
Week 40; n=8	1.319 (± 0.5782)			
Week 48; n=5	1.502 (± 0.7680)			

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate aminotransferase-to-platelet ratio index (APRI) Values Over Time: Cohorts 1/1b

End point title	Aspartate aminotransferase-to-platelet ratio index (APRI) Values Over Time: Cohorts 1/1b[13]

End point description:

APRI is calculated as 100*(aspartate aminotransferase/40) / platelets
The aspartate aminotransferase to platelet ratio index suggests the level of hepatic fibrosis and possible liver disease. Scores indicate the following:
< 0.5: fibrosis is ruled out
0.5 – 0.7: Associated with some kind of liver damage
0.7 - 1: Significant fibrosis
> 1: Associated with cirrhosis

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2 (24-48 hr post-dose), Week 2, Week 4, Week 4 (24-48 hr post-dose), Week 6, Week 16, Week 16 (24-48 hr post-dose), Week 24

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: numerical score				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=4, 4	0.485 (± 0.2249)	0.745 (± 0.3877)		
Day 2 (24-48 hr post-dose); n=4, 4	0.463 (± 0.2133)	0.753 (± 0.3923)		
Week 2; n=4, 4	0.633 (± 0.3349)	0.910 (± 0.5231)		

Week 4; n=4, 4	0.463 (± 0.2185)	0.810 (± 0.4031)		
Week 4 (24-48 hr post-dose); n=4, 4	0.468 (± 0.1921)	0.785 (± 0.4171)		
Week 6; n=4, 4	0.433 (± 0.1688)	0.918 (± 0.1834)		
Week 16; n=3, 4	0.343 (± 0.0404)	0.555 (± 0.3008)		
Week 16 (24-48 hr post-dose); n=3, 3	0.330 (± 0.0700)	0.603 (± 0.4203)		
Week 24; n=4, 4	0.310 (± 0.0970)	0.513 (± 0.2892)		

Statistical analyses

No statistical analyses for this end point

Secondary: APRI Values Over Time: Cohort 2

End point title	APRI Values Over Time: Cohort 2[14]

End point description:

APRI is calculated as 100*(aspartate aminotransferase/40) / platelets
The aspartate aminotransferase to platelet ratio index suggests the level of hepatic fibrosis and possible liver disease. Scores indicate the following:
< 0.5: fibrosis is ruled out
0.5 – 0.7: Associated with some kind of liver damage
0.7 - 1: Significant fibrosis
> 1: Associated with cirrhosis

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2 (24-48 hr post-dose), Week 2, Week 4, Week 4 (24-48 hr post-dose), Week 6, Week 16, Week 16 (24-48 hr post-dose), Week 22, Week 28, Week 34, Week 40, Week 48

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: numerical score				
arithmetic mean (standard deviation)				
Baseline (Day 1); n=8	0.500 (± 0.2102)			
Day 2 (24-48 hr post-dose); n=8	0.515 (± 0.2023)			
Week 2; n=7	0.486 (± 0.1551)			
Week 4; n=8	0.479 (± 0.2226)			
Week 4 (24-48 hr post-dose); n=8	0.454 (± 0.2127)			

Week 6; n=7	0.463 (± 0.1678)			
Week 16; n=8	0.372 (± 0.1812)			
Week 16 (24-48 hr post-dose); n=8	0.358 (± 0.2160)			
Week 22; n=8	0.386 (± 0.2011)			
Week 28; n=7	0.387 (± 0.2642)			
Week 34; n=7	0.379 (± 0.2449)			
Week 40; n=8	0.349 (± 0.1768)			
Week 48; n=5	0.440 (± 0.2310)			

Statistical analyses

No statistical analyses for this end point

Secondary: N-Terminal Type III Collagen Propeptide (PRO-C3) Values Over Time: Cohorts 1/1b

End point title	N-Terminal Type III Collagen Propeptide (PRO-C3) Values Over Time: Cohorts 1/1b[15]

End point description:

PRO-C3 may be a biomarker for the formation of fibrotic tissue in the liver. For serum, the normal range is 6.1 – 13.8 ng/mL (based on a study of human serum samples from healthy men and women). Due to ethnic, dietary and age variations, the reference limits given may not apply to all populations. A reduction in Pro-C3 over time may indicate a reduction in hepatic fibrogenesis.

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 16, 24

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: µg/L				
arithmetic mean (standard deviation)				
Baseline	16.78 (± 2.960)	25.15 (± 9.310)		
Week 4	16.90 (± 3.539)	22.10 (± 7.202)		
Week 16	15.60 (± 1.818)	19.30 (± 0.245)		
Week 24	18.08 (± 2.159)	16.63 (± 1.621)		

Statistical analyses

No statistical analyses for this end point

Secondary: PRO-C3 Values Over Time: Cohort 2

End point title	PRO-C3 Values Over Time: Cohort 2[16]

End point description:

PRO-C3 may be a biomarker for the formation of fibrotic tissue in the liver. For serum, the normal range is 6.1 – 13.8 ng/mL (based on a study of human serum samples from healthy men and women). Due to ethnic, dietary and age variations, the reference limits given may not apply to all populations. A reduction in Pro-C3 over time may indicate a reduction in hepatic fibrogenesis.

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 16, 28, 40, 48

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: µg/L				
arithmetic mean (standard deviation)				
Baseline	18.21 (± 3.002)			
Week 4	15.81 (± 2.948)			
Week 16	17.03 (± 2.463)			
Week 28	14.31 (± 2.362)			
Week 40	15.10 (± 2.989)			
Week 48	17.09 (± 7.967)			

Statistical analyses

No statistical analyses for this end point

Secondary: FibroScan® Values Over Time: Cohorts 1/1b

End point title	FibroScan® Values Over Time: Cohorts 1/1b[17]

End point description:

FibroScan is a type of liver elastography. Normal results are usually between 2 and 7 kilopascals (kPa), with results higher than the normal range if liver disease is present. The highest possible result is 75 kPa.

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: kPa				
arithmetic mean (standard deviation)				
Baseline	7.28 (± 2.632)	12.70 (± 6.988)		
Week 24	7.30 (± 3.730)	10.55 (± 5.802)		

Statistical analyses

No statistical analyses for this end point

Secondary: FibroScan® Values Over Time: Cohort 2

End point title	FibroScan® Values Over Time: Cohort 2[18]

End point description:

FibroScan is a type of liver elastography. Normal results are usually between 2 and 7 kilopascals (kPa), with results higher than the normal range if liver disease is present. The highest possible result is 75 kPa.

Safety Analysis Set: all participants who received at least one dose of study drug; n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline, Week 48

Notes:

[18] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: kPa				
arithmetic mean (standard deviation)				
Baseline; n=8	9.89 (± 3.205)			
Week 48; n=7	8.67 (± 3.263)			

Statistical analyses

No statistical analyses for this end point

Secondary: Portal Inflammation Over Time: Cohorts 1/1b

End point title	Portal Inflammation Over Time: Cohorts 1/1b[19]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of portal inflammation, which was scored on a scale from 0 (none) to 3 (severe).

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[19] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	25.0	50.0		
no change	50.0	50.0		
≥ 1-point worsening	25.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Portal Inflammation Over Time: Cohort 2

End point title	Portal Inflammation Over Time: Cohort 2[20]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of portal inflammation, which was scored on a scale from 0 (none) to 3 (severe).

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 48

Notes:

[20] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	12.5			
no change	37.5			
≥ 1-point worsening	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Interface Hepatitis Over Time: Cohorts 1/1b

End point title	Interface Hepatitis Over Time: Cohorts 1/1b[21]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of interface hepatitis, which was scored on a scale from 0 (none) to 3 (severe).

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[21] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	50.0	0.0		
no change	0.0	100.0		
≥ 1-point worsening	25.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Interface Hepatitis Over Time: Cohort 2

End point title	Interface Hepatitis Over Time: Cohort 2[22]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of interface hepatitis, which was scored on a scale from 0 (none) to 3 (severe).

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 48

Notes:

[22] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	25.0			
no change	25.0			
≥ 1-point worsening	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Lobular Inflammation Over Time: Cohorts 1/1b

End point title	Lobular Inflammation Over Time: Cohorts 1/1b[23]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of lobular inflammation, which was scored on a scale from 0 (none) to 3 (severe).

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[23] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	0.0	0.0		
no change	25.0	50.0		
≥ 1-point worsening	50.0	50.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Lobular Inflammation Over Time: Cohort 2

End point title	Lobular Inflammation Over Time: Cohort 2[24]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of lobular inflammation, which was scored on a scale from 0 (none) to 3 (severe).

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 48

Notes:

[24] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	0.0			
no change	62.5			
≥ 1-point worsening	12.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatocyte Cell Death Over Time: Cohorts 1/1b

End point title	Hepatocyte Cell Death Over Time: Cohorts 1/1b[25]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of hepatocyte cell death. Hepatocyte Cell Death Score: 0 = No acidophil bodies; 1 = Few acidophil bodies; 2 = Many acidophil.

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[25] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	0.0	0.0		
no change	25.0	0.0		
≥ 1-point worsening	25.0	25.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatocyte cell death Over Time: Cohort 2

End point title	Hepatocyte cell death Over Time: Cohort 2[26]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the liver biopsy parameter of hepatocyte cell death. Hepatocyte Cell Death Score: 0 = No acidophil bodies; 1 = Few acidophil bodies; 2 = Many acidophil.

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 48

Notes:

[26] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	0.0			
no change	62.5			
≥ 1-point worsening	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: METAVIR Fibrosis Stage Score Over Time: Cohorts 1/1b

End point title	METAVIR Fibrosis Stage Score Over Time: Cohorts 1/1b[27]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the METAVIR fibrosis stage score. The METAVIR scoring system is a system used to assess the extent of inflammation and fibrosis by histopathological evaluation in a liver biopsy of patients with hepatitis C. The stage represents the amount of fibrosis or scarring.

F0: no fibrosis
F1: portal fibrosis without septa
F2: portal fibrosis with few septa
F3: numerous septa without cirrhosis
F4: cirrhosis

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[27] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	0.0	50.0		
no change	100.0	50.0		
≥ 1-point worsening	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: METAVIR Fibrosis Stage Score Over Time: Cohort 2

End point title	METAVIR Fibrosis Stage Score Over Time: Cohort 2[28]

End point description:

Percent of participants having ≥ 1-point improvement from baseline, no change from baseline, and ≥ 1-point worsening from the baseline category in the METAVIR fibrosis stage score. The METAVIR scoring system is a system used to assess the extent of inflammation and fibrosis by histopathological evaluation in a liver biopsy of patients with hepatitis C. The stage represents the amount of fibrosis or scarring.

F0: no fibrosis
F1: portal fibrosis without septa
F2: portal fibrosis with few septa
F3: numerous septa without cirrhosis
F4: cirrhosis

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 48

Notes:

[28] - 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: Endpoints are presented by individual cohort per protocol.

End point values	ARO-AAT 200 mg Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
≥ 1-point improvement	50.0			
no change	12.5			
≥ 1-point worsening	25.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point description:

An Adverse Event (AE) is any untoward medical occurrence which does not necessarily have to have a causal relationship with this treatment. Serious Adverse Event (SAE) is an AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, Is a congenital anomaly/birth defect, Is a medically important event or reaction. TEAEs are AEs with onset after administration of the study drug, or when a preexisting medical condition increases in severity or frequency after study drug administration. Not related events include those reported as 'Not Related' to study drug. Related events include those reported as 'Possibly Related' or 'Probably Related' to study drug.

Safety Analysis Set: all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

For a maximum duration of study follow-up of 202 weeks.

End point values	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1	ARO-AAT 200 mg Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	8	
Units: participants				
≥ 1 TEAE	4	4	8	
≥ 1 Serious TEAE	0	3	5	
TEAE Severity = Mild	3	1	2	
TEAE Severity = Moderate	1	3	4	
TEAE Severity = Severe	0	0	2	
TEAE = Not Related to Study Drug (SD)	1	2	3	
TEAE = Related to SD	3	2	5	
TEAE Injection Site Reaction (ISR) Severity = Mild	2	1	3	
TEAE ISR Severity = Moderate	0	0	1	
TEAE ISR Severity = Severe	0	0	0	
TEAE Leading to SD Discontinuation	0	0	0	
TEAE Requiring Dose Interruption of SD	0	1	3	
TEAE Leading to PRematurе Withdrawal From Study	0	0	0	
TEAE Causing Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: For a maximum duration of study follow-up of 202 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	ARO-AAT 100 mg Cohort 1b
Reporting group description: Primary Study Period (6-12 months): 100 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods. Treatment Extension I (12 months): 100 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W). Treatment Extension II (up to 24 Months): 100 mg dose of subcutaneous ARO-AAT Q12W. The maximum number of doses for participants completing the treatment extension periods was 15 doses.	
Reporting group title	ARO-AAT 200 mg Cohort 1
Reporting group description: Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 3 doses, with 2 optional treatment extension periods. Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W). Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W. The maximum number of doses for participants completing the treatment extension periods was 15 doses.	
Reporting group title	ARO-AAT 200 mg Cohort 2
Reporting group description: Primary Study Period (6-12 months): 200 mg dose of subcutaneous ARO-AAT for a minimum of 5 doses, with optional treatment extension periods. Treatment Extension I (12 months): 200 mg dose of subcutaneous ARO-AAT every 12 weeks (Q12W). Treatment Extension II (up to 24 Months): 200 mg dose of subcutaneous ARO-AAT Q12W. The maximum number of doses for participants completing the treatment extension periods was 17 doses.	

Serious adverse events	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1	ARO-AAT 200 mg Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	4 / 4 (100.00%)	5 / 8 (62.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pneumothorax			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Diverticulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral myocarditis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ARO-AAT 100 mg Cohort 1b	ARO-AAT 200 mg Cohort 1	ARO-AAT 200 mg Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	8 / 8 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	3
Hypertensive crisis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Dental implantation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	3 / 8 (37.50%)
occurrences (all)	1	0	3
Injection site reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	7
Fatigue			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	2
Injection site bruising			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injection site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injection site inflammation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injection site pruritus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Social circumstances			
Denture wearer			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	2
Chronic obstructive pulmonary			

disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Respiratory disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sleep apnoea syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Productive cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Loss of libido			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	2 / 8 (25.00%)
occurrences (all)	2	2	2
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Blood potassium increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
C-reactive protein increased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Coagulation test abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Heart rate irregular			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Spirometry abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vaccination complication			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Wound			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Arthropod sting			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	1
Headache			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	1 / 8 (12.50%)
occurrences (all)	1	2	2
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	2
Sciatica			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Piriformis syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Eye disorders			

Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	3
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	3
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Oesophageal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hyperhidrosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Renal and urinary disorders			
Incontinence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	3 / 8 (37.50%)
occurrences (all)	1	0	3
Arthralgia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	2 / 8 (25.00%)
occurrences (all)	3	1	4
Bursitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Arthritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Plantar fasciitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 4 (75.00%)	4 / 4 (100.00%)	6 / 8 (75.00%)
occurrences (all)	9	16	13
COVID-19			
subjects affected / exposed	3 / 4 (75.00%)	3 / 4 (75.00%)	4 / 8 (50.00%)
occurrences (all)	3	4	5
Anal candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Candida infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hepatitis E			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	3
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Coronavirus infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Osteomyelitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Otitis media			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pulpitis dental			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Tooth infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2019	OVERVIEW/RATIONALE: 1. The protocol was amended in response to recommendations based on review by the Medicines and Healthcare Products Regualtory Agency (MHRA). 2. Correction of administrative, grammatical, formatting errors and inconsistencies; rewording for clarity.
10 March 2020	OVERVIEW/RATIONALE: 1. The protocol was amended to include cohort 1b at 100mg (N=4) as well as to add the inclusion of patients with Metavir F1 fibrosis or equivalent. • A 100mg cohort was added to compare with the 200mg cohort to see if study endpoints may have a dose response relationship. • An F1 fibrosis score (or equivalent) will be allowed as the study endpoints are now considered to be independent of the need to have Metavir fibrosis F2 and F3, or equivalent. 2. Correction of administrative, grammatical, formatting errors and inconsistencies; rewording for clarity.
14 October 2020	OVERVIEW/RATIONALE: 1. The primary endpoint has been revised to evaluation of change (from baseline over time) in total, soluble and insoluble Z-AAT concentrations in the liver of study patients. The primary rationale for protocol version 4.0 is to better align primary and secondary endpoints with the stated purpose of the study. This is an open label pilot study, intended to evaluate various pharmacodynamic markers as well as to explore treatment effect variability with different treatment durations (e.g. biopsy at approximately 6, 12, 18- and 24-months post-dose). This will help to inform on the length of treatment required in later stage studies. A histologic AATD liver disease activity scale was originally proposed as a primary endpoint. This was a placeholder endpoint as sponsor was investigating the development of a histologic grading scale of liver disease severity in AATD patients. While histologic endpoints are still included, in protocol version 4.0 the primary endpoint has been changed to liver Z-AAT protein. Liver Z-AAT has been thoroughly described as the causative factor of AATD liver disease and liver Z-AAT protein correlates with severity of liver fibrosis and with clinical outcomes. Intra-hepatic Z-AAT protein is also readily quantifiable using a validated assay and does not suffer from intra-reader or inter-reader variability as is the case for pathologist histologic evaluation. Thus, it is more likely to reliably identify differences in pharmacodynamic effect with different treatment durations. Additionally, histologic characteristics found in AATD liver disease (e.g. peri-portal inflammation, steatosis) overlap with those found in other common liver diseases such as NAFLD and NASH which may not respond to ARO-AAT and may confound evaluation of treatment effect. In contrast, intra-hepatic Z-AAT protein is only present in the livers of patients with AATD. For these reasons, liver Z-AAT is now the primary endpoint of the study.

14 October 2020	(continued) 2. Rationale for additional endpoint changes: • Serum Z-AAT levels have been shifted to the 1st secondary endpoint as serum levels correlate well with intra-hepatic total Z-AAT, consistent with the liver as the main source of serum AAT. • Changes in ALT and GGT were prioritized as secondary endpoints as these are clinically relevant biomarkers of liver disease and have been shown to associate with severity of liver disease in an AATD population (Clark et al., 2018). • Other non-invasive measures of liver fibrosis including FibroScan and Pro-C3 have also been shifted to secondary endpoints. Histologic parameters are still included as secondary endpoints and will be evaluated. • MRE has become more broadly available and is included as an additional exploratory assessment of liver fibrosis. • Consequently, the study title was also revised. 3. Correction of administrative, grammatical, formatting errors and inconsistencies; rewording for clarity.
10 February 2021	GENERAL OVERVIEW: 1. The Global Protocol has been amended to extend the Extension phase of the study by one year. For design clarity, the initial dosing period of the study is referred to as the Primary Study Period and the treatment extension period is referred to as Treatment Extension I and Treatment Extension II (12 month duration for each). 2. Correction of administrative, grammatical, formatting errors and inconsistencies; rewording for clarity. Major changes: 1. Protocol Synopsis: The study has been extended for an additional year to include a new Treatment Extension II after Week 44. Rationale: The extension period allows subjects to remain on continuous ARO-AAT treatment for long-term safety evaluation. During this period, subjects will have the option to continue to receive the same dose level of ARO-AAT Q12W for up to an additional 12 months or until they roll over into another long-term Extension study, whichever comes first. 2. Protocol Synopsis: Secondary Endpoint : Secondary Endpoint was revised to replace Ishak with Metavir. Rationale: Although both methods are recognized methods for evaluating fibrosis, Metavir has a smaller scale and is more widely used in clinical practice.
16 November 2021	(continued) GENERAL OVERVIEW: 1. The Global Protocol has been amended to extend the Extension II part of the study by one year. 2. Assessment of immunogenicity (Incidence of anti-drug antibodies (ADAs) to ARO-AAT) was added as a safety endpoint. 3. Collection of ADAs was added. 4. Correction of administrative, grammatical, formatting errors and inconsistencies; rewording for clarity. Major Changes: 1. Protocol Synopsis: Study Design/Methods: Extension II part of the study has been extended for an additional year. Rationale: The extension period allows subjects to remain on continuous ARO-AAT treatment for long-term safety evaluation. During this period, subjects will have the option to continue to receive the same dose level of ARO-AAT Q12W for up to an additional 12 months or until they roll over into another long-term Extension study, whichever comes first. 2. Protocol Synopsis: Secondary Endpoints: Assessment of immunogenicity (Incidence of anti-drug antibodies to ARO-AAT) was added as a safety endpoint. Rationale: Although results from a Phase I study (AROAAT1001) showed no evidence of drug-induced de novo formation of anti-ARO-AAT antibody formation after single or repeat doses of ARO-AAT in the healthy adult volunteers enrolled in study, anti-drug antibody (ADA) assessment has been added as a safety endpoint in study AROAAT2002. ADA was included to further evaluate the potential for immunogenicity following ARO-AAT treatment in patients with AATD.

21 July 2022	GENERAL OVERVIEW: 1. This global protocol has been amended to inform of fazirsiran dose selection by the Sponsor based on review of cumulative safety, efficacy, and pharmacodynamics data from the fazirsiran clinical program . The amendment specifies that all subjects continuing in Extension Treatment Period II will receive the selected fazirsiran dose (200 mg) following the respective country regulatory and ethics committees' approvals (including local approvals as necessary) of AROAAT2002 protocol amendment v7.0. As such, all ongoing subjects in Extension Treatment Period II will be consented and subjects in Cohort 1b (100 mg) will begin receiving the selected dose at the next scheduled dosing timepoint. 2. Pulmonary function test (PFT) text was updated to clarify instructions for performing spirometry and diffusing capacity for carbon monoxide (DLCO), to acknowledge acceptability of following bronchodilator administration as per site practice, and to describe specific PFT data to include on the electronic case report form (eCRF). 3. The repeat liver biopsy in the treatment extension period will be optional. 4. Vital signs measurement and electrocardiogram (ECG) assessment text was updated to clarify patient positioning during the assessments. 5. Methods sections were updated to change the current pre-dose window for assessments from 60 minutes to 3 hours. 6. Investigational product (IP) nomenclature was updated to include fazirsiran and TAK-999 (also referred to as ARO-AAT). Drug product nomenclature was updated to include Fazirsiran Injection. 7. Fazirsiran supply, preparation, storage, and labelling information was updated, and includes guidance on allowing the fazirsiran vial to come to room temperature before administration. 8. A new section was added to provide more detail on pregnancy reporting. 9. Text was revised to make administrative updates, correct grammatical and formatting errors and inconsistencies, update abbreviations, update references.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported