Clinical trial results:
A Placebo-Controlled, Multi-dose, Phase 2/3 Study to Determine the Safety, Tolerability and Effect on Liver Histologic Parameters in Response to ARO-AAT in Patients with Alpha-1 Antitrypsin Deficiency (AATD) [SEQUOIA]

Summary

EudraCT number	2018-003385-14
Trial protocol	IE SE ES GB PT NL DE AT IT
Global end of trial date	18 September 2023

Results information

Result version number	v1 (current)
This version publication date	04 October 2024
First version publication date	04 October 2024

Trial information

Trial identification

Sponsor protocol code	AROAAT2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03945292
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	Chief Operating Officer, Arrowhead Pharmaceuticals, Inc., 001 6263043400, info@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	18 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A:
• To select a single dose level for use in Part B of the study based on a combined evaluation of safety and pharmacodynamic dose response in each Part A cohort using change over time from baseline to Day 113 in serum Z-AAT levels

Part B:
• To evaluate efficacy (as assessed by the proportion of ARO-AAT treated patients relative to placebo achieving a 2-point improvement in a histologic grading scale of alpha-1 antitrypsin deficiency associated liver disease AND no worsening of liver fibrosis based on Ishak score on end of study biopsy).

Protection of trial subjects:

Prior to commencement of any Screening procedures, the Investigator, or designee, will inform the patient about the nature and purpose of the study, including the risks and benefits involved, possible AEs, the fact that their participation is voluntary and provide a copy of the IRB/EC-approved Informed Consent Form (ICF) for review. Each patient will acknowledge receipt of this information by giving written informed consent for their involvement in the study in the presence of the Investigator, or designee, who will also sign and date the ICF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	40
EEA total number of subjects	11

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)	35
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Following Screening, eligible participants were randomly allocated in a 2:1 ratio within each dose cohort, to receive one of 3 dose levels of fazirsiran (25, 100, or 200 mg) or placebo.

Period 1

Period 1 title	Randomized Double-Blind Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomization was performed within each dose cohort to maintain blinding due to different dose volumes in the double-blinded phase.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fazirsiran 25 mg

Arm description:

Participants with no fibrosis: Fazirsiran 25 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 25 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

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

Dosage and administration details:

Each single dose of active drug (fazirsiran) was administered by subcutaneous injection.

Arm title	Fazirsiran 100 mg

Arm description:

Participants with no fibrosis: Fazirsiran 100 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 100 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

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

Dosage and administration details:

Each single dose of active drug (fazirsiran) was administered by subcutaneous injection.

Arm title	Fazirsiran 200 mg

Arm description:

Participants with no fibrosis: Fazirsiran 200 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 200 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

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

Dosage and administration details:

Each single dose of active drug (fazirsiran) was administered by subcutaneous injection.

Arm title	Placebo

Arm description:

Participants with no fibrosis: Placebo administered on Day 1 and Week 4.

Participants with fibrosis: Placebo administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

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:

Each single dose placebo (normal saline 0.9%) was administered by subcutaneous injection.

Number of subjects in period 1	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg
Started	9	8	9
Completed	8	8	7
Not completed	1	0	2
Consent withdrawn by subject	1	-	1
Adverse event	-	-	1

Number of subjects in period 1	Placebo
Started	14
Completed	14
Not completed	0
Consent withdrawn by subject	-
Adverse event	-

Period 2

Period 2 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fazirsiran 25 mg DB/200 mg OL

Arm description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 25 mg and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

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

Dosage and administration details:

Each single dose of active drug (fazirsiran) was administered by subcutaneous injection.

Arm title	Fazirsiran 100 mg DB/200 mg OL

Arm description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 100 mg and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

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

Dosage and administration details:

Each single dose of active drug (fazirsiran) was administered by subcutaneous injection.

Arm title	Fazirsiran 200 mg DB/200 mg OL

Arm description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 200 mg and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

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

Dosage and administration details:

Each single dose of active drug (fazirsiran) was administered by subcutaneous injection.

Arm title	Placebo DB / Fazirsiran 200 mg OL

Arm description:

Participants with fibrosis at Screening who received double-blind (DB) placebo and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Arm type	Experimental

Investigational medicinal product name	Fazisiran injection
Investigational medicinal product code	ARO-AAT Injection
Other name	TAK-999 Injection
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each single dose of active drug (fazirsiran) was administered by subcutaneous injection.

Number of subjects in period 2[1]	Fazirsiran 25 mg DB/200 mg OL	Fazirsiran 100 mg DB/200 mg OL	Fazirsiran 200 mg DB/200 mg OL
Started	4	5	5
Completed	4	5	5
Not completed	0	0	0
Adverse event	-	-	-

Number of subjects in period 2[1]	Placebo DB / Fazirsiran 200 mg OL
Started	9
Completed	8
Not completed	1
Adverse event	1

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: Only participants entering the Open-Label Phase are presented in the second period.

Baseline characteristics

Reporting groups	
Reporting group title	Fazirsiran 25 mg
Reporting group description:	
Participants with no fibrosis: Fazirsiran 25 mg administered on Day 1 and Week 4. Participants with fibrosis: Fazirsiran 25 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.	

Reporting group title	Fazirsiran 100 mg
Reporting group description:	
Participants with no fibrosis: Fazirsiran 100 mg administered on Day 1 and Week 4. Participants with fibrosis: Fazirsiran 100 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.	

Reporting group title	Fazirsiran 200 mg
Reporting group description:	
Participants with no fibrosis: Fazirsiran 200 mg administered on Day 1 and Week 4. Participants with fibrosis: Fazirsiran 200 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.	

Reporting group title	Placebo
Reporting group description:	
Participants with no fibrosis: Placebo administered on Day 1 and Week 4. Participants with fibrosis: Placebo administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.	

Reporting group values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg
Number of subjects	9	8	9
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 52.6 ± 18.06	 47.9 ± 12.25	 51.6 ± 9.44
Gender categorical Units: Subjects			
Female	5	6	6
Male	4	2	3
Race Units: Subjects			
White	9	8	9
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Non-Hispanic or Latino	9	7	9
Fibrosis Status at Screening Units: Subjects			

Fibrosis at Screening	4	5	7
No fibrosis at Screening	5	3	2

Reporting group values	Placebo	Total	
Number of subjects	14	40	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 57.4 ± 9.05	 -	
Gender categorical Units: Subjects			
Female	5	22	
Male	9	18	
Race Units: Subjects			
White	14	40	
Ethnicity Units: Subjects			
Hispanic or Latino	2	3	
Non-Hispanic or Latino	12	37	
Fibrosis Status at Screening Units: Subjects			
Fibrosis at Screening	9	25	
No fibrosis at Screening	5	15	

End points

End points reporting groups

Reporting group title	Fazirsiran 25 mg

Reporting group description:

Participants with no fibrosis: Fazirsiran 25 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 25 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Fazirsiran 100 mg

Reporting group description:

Participants with no fibrosis: Fazirsiran 100 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 100 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Fazirsiran 200 mg

Reporting group description:

Participants with no fibrosis: Fazirsiran 200 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 200 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Placebo

Reporting group description:

Participants with no fibrosis: Placebo administered on Day 1 and Week 4.

Participants with fibrosis: Placebo administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Fazirsiran 25 mg DB/200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 25 mg and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Reporting group title	Fazirsiran 100 mg DB/200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 100 mg and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Reporting group title	Fazirsiran 200 mg DB/200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 200 mg and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Reporting group title	Placebo DB / Fazirsiran 200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) placebo and who completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Subject analysis set title	Fazirsiran 25 mg: Participants With No Fibrosis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with no fibrosis: Fazirsiran 25 mg administered on Day 1 and Week 4.

Subject analysis set title	Fazirsiran 25 mg: Participants With Fibrosis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with fibrosis at baseline: Fazirsiran 25 mg administered on Day 1, Week 4, and Week 16,

then every 12 weeks up to 18 total doses.

Subject analysis set title	Fazirsiran 100 mg: Participants With No Fibrosis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with no fibrosis: Fazirsiran 100 mg administered on Day 1 and Week 4.	
Subject analysis set title	Fazirsiran 100 mg: Participants With Fibrosis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with fibrosis: Fazirsiran 100 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.	
Subject analysis set title	Fazirsiran 200 mg: Participants With No Fibrosis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with no fibrosis: Fazirsiran 200 mg administered on Day 1 and Week 4.	
Subject analysis set title	Fazirsiran 200 mg: Participants With Fibrosis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with fibrosis: Fazirsiran 200 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.	

Primary: Percent Change From Baseline in Serum Z-Alpha-1 Antitrypsin (Z-AAT) at Week 16

End point title	Percent Change From Baseline in Serum Z-Alpha-1 Antitrypsin (Z-AAT) at Week 16
End point description: Full Analysis Set: All randomized participants who received at least one dose of study drug.	
End point type	Primary
End point timeframe: Baseline, Week 16 (+/- 2 weeks)	

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	8	9	14
Units: percentage change				
least squares mean (standard error)	-62.17 (± 4.279)	-85.39 (± 4.634)	-92.93 (± 4.341)	4.64 (± 3.211)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fazirsiran 25 mg v Placebo

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Dfference
Point estimate	-66.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.18
upper limit	-56.45
Variability estimate	Standard error of the mean
Dispersion value	5.107

Notes:

[1] - From a mixed model with repeated measures, including fixed effects for treatment, week, treatment-by-week interaction, presence of metabolic syndrome, presence of NAFLD or NASH, baseline serum Z-AAT as covariate, and subject as a random effect.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fazirsiran 100 mg
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Dfference
Point estimate	-90.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100.72
upper limit	-79.34
Variability estimate	Standard error of the mean
Dispersion value	5.26

Notes:

[2] - From a mixed model with repeated measures, including fixed effects for treatment, week, treatment-by-week interaction, presence of metabolic syndrome, presence of NAFLD or NASH, baseline serum Z-AAT as covariate, and subject as a random effect.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v Fazirsiran 200 mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Dfference
Point estimate	-97.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	-108.21
upper limit	-86.94
Variability estimate	Standard error of the mean
Dispersion value	5.24

Notes:

[3] - From a mixed model with repeated measures, including fixed effects for treatment, week, treatment-by-week interaction, presence of metabolic syndrome, presence of NAFLD or NASH, baseline serum Z-AAT as covariate, and subject as a random effect.

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) in the Double-Blind Phase

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs) in the Double-Blind Phase

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. A 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/TESAEs are defined as those AEs that first occurred or worsened in severity following dose administration through end of study (EOS) or Early Termination or first dose of open-label phase fazirsiran.

Safety Analysis Set: All participants who receive at least one dose of study drug.

End point type	Secondary

End point timeframe:

Double Blind Phase: dose administration through end of study (EOS) or Early Termination or first dose of open-label phase fazirsiran.

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	8	9	14
Units: participants				
TEAEs	9	8	9	14
TESAEs	0	0	2	3
TEAEs Leading to Withdrawal of Study Drug	0	0	1	0
TEAEs Leading to Study Termination	0	0	1	0
TEAEs Leading to Death	0	0	0	0
TEAEs by Worst Severity: Mild	3	2	1	5
TEAEs by Worst Severity: Moderate	6	6	6	6
TEAEs by Worst Severity: Severe	0	0	2	3
TEAEs by Worst Relationship: Not Related	7	4	5	6
TEAEs by Worst Relationship: Possibly Related	2	3	1	8
TEAEs by Worst Relationship: Probably Related	0	1	3	0
TEAEs by Worst Relationship: Possibly or Probably	2	4	4	8
TEAE at Injection Site	1	1	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With TEAEs in the Open-Label Phase

End point title	Number of Participants With TEAEs in the Open-Label Phase

End point description:

An AE is any untoward medical occurrence, which does not necessarily have to have a causal relationship with this treatment. An 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/TESAEs are defined as those AEs that first occurred or worsened in severity following dose administration of the first dose of open-label phase fazirsiran through EOS or Early Termination.

Safety Analysis Set: All participants who receive at least one dose of study drug.

End point type	Secondary

End point timeframe:

From dose administration of the first dose of open-label phase fazirsiran through EOS or Early Termination

End point values	Fazirsiran 25 mg DB/200 mg OL	Fazirsiran 100 mg DB/200 mg OL	Fazirsiran 200 mg DB/200 mg OL	Placebo DB / Fazirsiran 200 mg OL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	5	9
Units: participants				
TEAEs	4	4	3	9
TESAEs	1	1	1	1
TEAEs Leading to Withdrawal of Study Drug	0	0	0	1
TEAEs Leading to Study Termination	0	0	0	1
TEAEs Leading to Death	0	0	0	0
TEAEs by Worst Severity: Mild	3	2	0	7
TEAEs by Worst Severity: Moderate	0	1	3	1
TEAEs by Worst Severity: Severe	1	1	0	1
TEAEs by Worst Relationship: Not Related	2	0	3	7
TEAEs by Worst Relationship: Possibly Related	2	3	0	2
TEAEs by Worst Relationship: Probably Related	0	1	0	0
TEAEs by Worst Relationship: Possibly or Probably	2	4	0	2
TEAE at Injection Site	1	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change from Baseline in Total Liver Z-AAT (Insoluble + Soluble) Protein at Post-dose Biopsy for Participants with Fibrosis

End point title	Absolute Change from Baseline in Total Liver Z-AAT (Insoluble + Soluble) Protein at Post-dose Biopsy for Participants with Fibrosis

End point description:

Post-dose biopsy includes all post-dose biopsy collected at Week 48 or Week 72 or Week 96.

Biopsy Analysis Set: All randomized participants who received at least one dose of study drug and had at least one central read histology biopsy result.

End point type	Secondary

End point timeframe:

Baseline, Post-dose Liver biopsy (at Week 48 [+/- 2 weeks], or Week 72 [+/- 4 weeks], or Week 96 [+/- 4 weeks])

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	7	8
Units: nmol/g				
arithmetic mean (standard deviation)	-89.341 (± 94.832)	-259.892 (± 330.199)	-29.371 (± 22.867)	-4.738 (± 57.342)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Total Liver Z-AAT (Insoluble + Soluble) Protein at Post-dose Biopsy for Participants with Fibrosis

End point title	Percent Change from Baseline in Total Liver Z-AAT (Insoluble + Soluble) Protein at Post-dose Biopsy for Participants with Fibrosis

End point description:

Post-dose biopsy includes all post-dose biopsy collected at Week 48 or Week 72 or Week 96.

Biopsy Analysis Set: All randomized participants who received at least one dose of study drug and had at least one central read histology biopsy result.

End point type	Secondary

End point timeframe:

Baseline, Post-dose Liver biopsy (at Week 48 [+/- 2 weeks], or Week 72 [+/- 4 weeks], or Week 96

[+/- 4 weeks])

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	7	8
Units: percentage change				
least squares mean (standard error)	-86.89 (± 29.658)	-81.61 (± 29.503)	-98.16 (± 23.256)	42.42 (± 21.133)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fazirsiran 25 mg v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [4]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-129.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-205.52
upper limit	-53.11
Variability estimate	Standard error of the mean
Dispersion value	36.409

Notes:

[4] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline total liver Z-AAT protein as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Fazirsiran 100 mg v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-124.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-201.9
upper limit	-46.15
Variability estimate	Standard error of the mean
Dispersion value	37.207

Notes:

[5] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline total liver Z-AAT protein as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v Fazirsiran 200 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-140.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-205.27
upper limit	-75.89
Variability estimate	Standard error of the mean
Dispersion value	30.906

Notes:

[6] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline total liver Z-AAT protein as a covariate.

Secondary: Absolute Change from Baseline in Liver Z-AAT Soluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point title	Absolute Change from Baseline in Liver Z-AAT Soluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point description:

Post-dose biopsy includes all post-dose biopsy collected at Week 48 or Week 72 or Week 96.

Biopsy Analysis Set: All randomized participants who received at least one dose of study drug and had at least one central read histology biopsy result.

End point type	Secondary

End point timeframe:

Baseline, at Post-dose biopsy (Week 48 [+/- 2 weeks], or Week 72 [+/- 4 weeks], or Week 96 [+/- 4 weeks])

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	7	8
Units: nmol/g				
arithmetic mean (standard deviation)	-20.427 (± 15.042)	-109.747 (± 135.114)	-17.418 (± 4.860)	2.300 (± 12.940)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Z-AAT Soluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point title	Percent Change from Baseline in Liver Z-AAT Soluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point description:

Post-dose biopsy includes all post-dose biopsy collected at Week 48 or Week 72 or Week 96.

Biopsy Analysis Set: All randomized participants who received at least one dose of study drug and had at least one central read histology biopsy result.

End point type	Secondary

End point timeframe:

Baseline, Post-dose Biopsy (Week 48 [+/- 2 weeks], or Week 72 [+/- 4 weeks], or Week 96 [+/- 4 weeks])

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	7	8
Units: percentage change				
least squares mean (standard error)	-75.73 (± 16.645)	-87.23 (± 17.064)	-95.71 (± 12.824)	22.33 (± 11.890)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fazirsiran 25 mg v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-98.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-140.53
upper limit	-55.6
Variability estimate	Standard error of the mean
Dispersion value	20.291

Notes:

[7] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline soluble liver Z-AAT protein as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fazirsiran 100 mg

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-109.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-154.81
upper limit	-64.32
Variability estimate	Standard error of the mean
Dispersion value	21.616

Notes:

[8] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline soluble liver Z-AAT protein as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v Fazirsiran 200 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-118.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-153.95
upper limit	-82.12
Variability estimate	Standard error of the mean
Dispersion value	17.16

Notes:

[9] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline soluble liver Z-AAT protein as a covariate.

Secondary: Absolute Change from Baseline in Liver Z-AAT Insoluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point title	Absolute Change from Baseline in Liver Z-AAT Insoluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point description:

Post-dose biopsy includes all post-dose biopsy collected at Week 48 or Week 72 or Week 96.

Biopsy Analysis Set: All randomized participants who received at least one dose of study drug and had at least one central read histology biopsy result.

End point type	Secondary

End point timeframe:

Baseline, Post-dose Biopsy (Week 48 [+/- 2 weeks], or Week 72 [+/- 4 weeks], or Week 96 [+/- 4 weeks])

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	7	8
Units: nmol/g				
arithmetic mean (standard deviation)	-68.914 (± 80.725)	-150.145 (± 196.675)	-11.953 (± 18.602)	-7.038 (± 47.041)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Z-AAT Insoluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point title	Percent Change from Baseline in Liver Z-AAT Insoluble Protein at Post-dose Biopsy for Participants with Fibrosis

End point description:

Post-dose biopsy includes all post-dose biopsy collected at Week 48 or Week 72 or Week 96.

Biopsy Analysis Set: All randomized participants who received at least one dose of study drug and had at least one central read histology biopsy result.

End point type	Secondary

End point timeframe:

Baseline, Post-dose Biopsy (Week 48 [+/- 2 weeks], or Week 72 [+/- 4 weeks], or Week 96 [+/- 4 weeks])

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	7	8
Units: percentage change				
least squares mean (standard error)	-86.36 (± 60.305)	-72.44 (± 58.358)	-101.85 (± 47.495)	91.35 (± 42.750)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fazirsiran 25 mg v Placebo

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0247 [10]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-180.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-335.77
upper limit	-25.64
Variability estimate	Standard error of the mean
Dispersion value	74.087

Notes:

[10] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline insoluble liver Z-AAT protein as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Fazirsiran 100 mg
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0382 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-163.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-317.65
upper limit	-9.93
Variability estimate	Standard error of the mean
Dispersion value	73.513

Notes:

[11] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline insoluble liver Z-AAT protein as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v Fazirsiran 200 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0064 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-193.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-325.25
upper limit	-61.15

Variability estimate	Standard error of the mean
Dispersion value	63.089

Notes:

[12] - Model based summary statistics are from an analysis of covariance (ANCOVA) model with fixed effect factors treatment group and baseline insoluble liver Z-AAT protein as a covariate.

Secondary: Absolute Change from Baseline in Liver Function Tests: Alanine Aminotransferase (ALT) at Week 16 and Over Time Through End of Study (EOS)

End point title	Absolute Change from Baseline in Liver Function Tests: Alanine Aminotransferase (ALT) at Week 16 and Over Time Through End of Study (EOS)

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[13]	8[14]	9[15]	14[16]
Units: U/L				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	-3.0 (± 9.17)	-2.4 (± 5.42)	-8.4 (± 15.88)	1.7 (± 6.60)
Week 16 24 H; n=3, 4, 6, 9	-7.3 (± 11.93)	-3.8 (± 3.59)	-2.2 (± 2.86)	0.8 (± 5.31)
Week 28; n=7, 8, 9, 14	-10.7 (± 4.57)	-5.8 (± 9.56)	0.6 (± 6.48)	1.0 (± 6.91)
Week 40; n=8, 8, 9, 14	-4.6 (± 9.07)	-5.0 (± 8.78)	3.1 (± 9.79)	-0.1 (± 4.66)
PDLB at Week 48; n=4, 3, 6, 6	-10.5 (± 10.47)	0.0 (± 16.00)	-2.2 (± 5.31)	3.3 (± 7.71)
Week 52; n=8, 8, 9, 13	-1.5 (± 12.31)	-6.0 (± 7.39)	12.3 (± 33.80)	-0.4 (± 4.44)
Week 64; n=4, 4, 7, 9	-9.8 (± 8.50)	-14.3 (± 8.88)	-0.3 (± 8.30)	5.7 (± 15.48)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-6.0 (± 999999)
Week 76; n=3, 4, 6, 6	-7.3 (± 3.06)	-14.8 (± 9.07)	3.5 (± 8.24)	7.7 (± 8.85)
Week 88; n=3, 2, 5, 5	-9.0 (± 3.46)	-18.5 (± 9.19)	4.8 (± 4.97)	6.2 (± 7.76)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-21.0 (± 5.66)	12.0 (± 999999)	10.0 (± 12.73)
Week 100; n=2, 2, 2, 4	-9.0 (± 2.83)	-21.5 (± 9.19)	7.5 (± 7.78)	1.3 (± 9.43)
Week 112; n=1, 2, 2, 3	-8.0 (± 99999)	-18.0 (± 7.07)	8.0 (± 4.24)	-0.3 (± 6.43)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-18.0 (± 4.24)	7.0 (± 999999)	5.0 (± 11.53)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	4.0 (± 999999)	8.3 (± 17.90)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	11.0 (± 999999)	4.3 (± 14.98)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	23.0 (± 4.24)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-2.0 (± 9.90)	99999 (± 99999)

End of Study; n=3, 2, 2, 5	7.0 (± 16.64)	-1.0 (± 5.66)	-0.5 (± 4.95)	-0.2 (± 5.45)

Notes:

[13] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[14] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[15] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[16] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Function Tests: ALT at Week 16 and Over Time Through EOS

End point title	Percent Change from Baseline in Liver Function Tests: ALT at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[17]	8[18]	9[19]	14[20]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	-9.6 (± 20.1)	-4.3 (± 19.9)	-15.3 (± 16.2)	5.8 (± 16.1)
Week 16 24 H; n=3, 4, 6, 9	-15.7 (± 24.8)	-9.7 (± 8.9)	-10.8 (± 17.6)	0.5 (± 13.3)
Week 28; n=7, 8, 8, 14	-27.4 (± 8.5)	-12.4 (± 25.1)	2.0 (± 29.3)	6.4 (± 21.9)
Week 40; n=8, 8, 9, 14	-11.2 (± 21.4)	-13.0 (± 24.0)	4.0 (± 20.0)	2.9 (± 18.3)
PDLB at Week 48; n=4, 3, 6, 6	-21.7 (± 19.1)	-1.2 (± 38.2)	-4.8 (± 20.5)	5.9 (± 15.2)
Week 52; n=8, 8, 9, 13	-1.6 (± 32.9)	-15.2 (± 18.1)	14.5 (± 28.5)	-1.4 (± 14.8)
Week 64; n=4, 4, 7, 9	-22.3 (± 20.3)	-33.3 (± 15.5)	4.4 (± 35.8)	11.0 (± 29.3)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-14.3 (± 999999)
Week 76; n=3, 4, 6, 6	-20.0 (± 7.0)	-33.7 (± 16.2)	24.6 (± 43.6)	26.3 (± 34.1)
Week 88; n=3, 2, 5, 5	-24.1 (± 0.0)	-39.8 (± 15.9)	28.2 (± 32.6)	20.7 (± 28.6)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-45.7 (± 7.5)	60.0 (± 999999)	44.8 (± 58.7)
Week 100; n=2, 2, 2, 4	-31.0 (± 9.8)	-46.4 (± 15.2)	38.1 (± 38.1)	9.9 (± 24.1)
Week 112; n=1, 2, 2, 3	-27.6 (± 999999)	-38.9 (± 11.3)	41.4 (± 19.2)	3.3 (± 24.7)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-39.3 (± 5.1)	35.0 (± 999999)	25.2 (± 49.4)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	20.0 (± 999999)	40.1 (± 79.4)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	55.0 (± 999999)	25.5 (± 61.4)

Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	88.8 (± 3.0)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-10.3 (± 65.0)	99999 (± 99999)
End of Study; n=3, 2, 2, 5	14.1 (± 38.7)	-6.8 (± 34.6)	-8.4 (± 15.0)	4.7 (± 23.3)

Notes:

[17] - 99999=0 participants analyzed; 999999=1 participant analyzed

[18] - 99999=0 participants analyzed; 999999=1 participant analyzed

[19] - 99999=0 participants analyzed; 999999=1 participant analyzed

[20] - 99999=0 participants analyzed; 999999=1 participant analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change from Baseline in Liver Function Tests: Aspartate Aminotransferase (AST) at Week 16 and Over Time Through EOS

End point title	Absolute Change from Baseline in Liver Function Tests: Aspartate Aminotransferase (AST) at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[21]	8[22]	9[23]	14[24]
Units: U/L				
arithmetic mean (standard deviation)				
Week 16; n=9, 7, 8, 13	-2.9 (± 8.27)	-0.1 (± 4.02)	1.1 (± 6.10)	0.7 (± 5.23)
Week 16 24 H; n=3, 4, 6, 9	-7.7 (± 11.59)	0.0 (± 2.58)	0.3 (± 3.93)	-0.4 (± 3.81)
Week 28; n=8, 8, 9, 14	-7.4 (± 7.31)	-1.3 (± 4.68)	10.2 (± 27.92)	0.1 (± 5.49)
Week 40; n=8, 8, 9, 14	-2.9 (± 10.78)	2.0 (± 17.55)	2.9 (± 8.25)	-0.9 (± 3.65)
PDLB at Week 48; n=4, 3, 6, 6	-12.0 (± 10.42)	1.7 (± 4.16)	-1.0 (± 5.22)	1.2 (± 6.40)
Week 52; n=8, 8, 9, 13	-2.1 (± 9.89)	-0.9 (± 8.46)	6.3 (± 15.92)	-0.9 (± 2.93)
Week 64; n=4, 4, 7, 9	-8.8 (± 10.24)	-10.3 (± 10.40)	-0.7 (± 4.42)	1.9 (± 7.70)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-3.0 (± 999999)
Week 76; n=3, 4, 6, 6	-6.3 (± 4.73)	-10.3 (± 8.85)	3.2 (± 5.78)	7.5 (± 7.20)
Week 88; n=3, 2, 5, 5	-6.7 (± 5.69)	-16.5 (± 12.02)	3.8 (± 8.29)	4.2 (± 6.57)
PDLB at Week 96; n=0, 1, 1, 2	99999 (± 99999)	-11.0 (± 999999)	2.0 (± 999999)	5.0 (± 5.66)
Week 100; n=2, 2, 2, 4	-7.5 (± 2.12)	-21.5 (± 13.44)	1.5 (± 2.12)	0.0 (± 4.76)

Week 112; n=1, 2, 2, 3	-10.0 (± 999999)	-19.0 (± 14.14)	0.5 (± 0.71)	-2.0 (± 7.00)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-16.5 (± 10.61)	-1.0 (± 999999)	2.7 (± 9.29)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	-2.0 (± 999999)	6.7 (± 10.60)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	2.0 (± 999999)	1.0 (± 11.14)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	10.5 (± 0.71)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-1.5 (± 4.95)	99999 (± 99999)
End of Study; n=3, 2, 2, 5	4.7 (± 8.33)	1.5 (± 6.36)	1.5 (± 9.19)	-0.2 (± 3.96)

Notes:

[21] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[22] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[23] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[24] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Function Tests: AST at Week 16 and Over Time Through EOS

End point title	Percent Change from Baseline in Liver Function Tests: AST at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[25]	8[26]	9[27]	14[28]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 16; n=9, 7, 8, 13	-8.3 (± 20.0)	2.6 (± 16.4)	3.5 (± 22.5)	2.5 (± 14.3)
Week 16 24 H; n=3, 4, 6, 9	-16.9 (± 24.2)	0.4 (± 7.8)	1.5 (± 17.6)	0.1 (± 9.8)
Week 28; n=8, 8, 9, 14	-19.3 (± 19.3)	-0.9 (± 14.5)	26.8 (± 68.8)	3.2 (± 17.4)
Week 40; n=8, 8, 9, 14	-4.7 (± 26.9)	10.6 (± 43.4)	8.3 (± 21.7)	-1.0 (± 11.4)
PDLB at Week 48; n=4, 3, 6, 6	-27.1 (± 20.1)	6.0 (± 12.5)	-2.0 (± 16.2)	3.4 (± 19.2)
Week 52; n=8, 8, 9, 13	-4.1 (± 27.2)	1.9 (± 20.9)	17.3 (± 40.3)	-2.8 (± 9.7)
Week 64; n=4, 4, 7, 9	-20.5 (± 23.3)	-21.4 (± 15.4)	-2.6 (± 16.8)	9.5 (± 21.6)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-5.9 (± 999999)
Week 76; n=3, 4, 6, 6	-17.1 (± 12.7)	-22.2 (± 13.9)	11.9 (± 22.6)	30.3 (± 32.8)

Week 88; n=3, 2, 5, 5	-16.4 (± 10.1)	-30.6 (± 15.7)	18.1 (± 34.7)	21.1 (± 29.6)
PDLB at Week 96; n=0, 1, 1, 2	99999 (± 99999)	-26.8 (± 999999)	7.4 (± 999999)	31.9 (± 39.8)
Week 100; n=2, 2, 2, 4	-24.6 (± 9.1)	-40.5 (± 15.8)	5.6 (± 7.9)	5.2 (± 16.3)
Week 112; n=1, 2, 2, 3	-34.5 (± 999999)	-35.1 (± 18.7)	2.5 (± 3.5)	2.8 (± 27.0)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-31.0 (± 12.8)	-3.7 (± 999999)	25.6 (± 53.1)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	-7.4 (± 999999)	39.6 (± 70.4)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	7.4 (± 999999)	21.8 (± 56.6)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	55.2 (± 25.7)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-7.3 (± 26.9)	99999 (± 99999)
End of Study; n=3, 2, 2, 5	13.7 (± 24.6)	10.5 (± 35.1)	-2.7 (± 31.5)	0.7 (± 17.1)

Notes:

[25] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[26] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[27] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[28] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change from Baseline in Liver Function Tests: Alkaline Phosphatase (ALP) at Week 16 and Over Time Through EOS

End point title	Absolute Change from Baseline in Liver Function Tests: Alkaline Phosphatase (ALP) at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[29]	8[30]	9[31]	14[32]
Units: U/L				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	-2.8 (± 9.98)	-4.3 (± 6.50)	-13.8 (± 14.26)	4.9 (± 13.02)
Week 16 24 H; n=3, 4, 6, 9	-9.7 (± 8.62)	-1.0 (± 2.16)	-11.7 (± 14.83)	3.6 (± 6.62)
Week 28; n=8, 8, 9, 14	0.6 (± 12.29)	-4.9 (± 6.88)	-8.4 (± 13.53)	0.7 (± 5.51)
Week 40; n=8, 8, 9, 14	-1.1 (± 15.51)	-7.1 (± 6.36)	-8.3 (± 11.38)	1.6 (± 7.43)

PDLB at Week 48; n=4, 3, 6, 6	-10.5 (± 16.62)	-0.3 (± 1.15)	-2.8 (± 15.69)	1.2 (± 2.56)
Week 52; n=8, 8, 9, 13	-3.0 (± 15.38)	-7.6 (± 8.26)	-3.9 (± 9.36)	1.9 (± 6.01)
Week 64; n=4, 4, 7, 9	-8.3 (± 22.23)	-6.5 (± 8.96)	0.4 (± 15.66)	2.1 (± 9.25)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	5.0 (± 999999)
Week 76; n=3, 4, 6, 6	-14.0 (± 23.39)	-9.0 (± 11.58)	0.5 (± 11.50)	6.5 (± 11.33)
Week 88; n=3, 2, 5, 5	-14.7 (± 21.13)	-16.5 (± 23.33)	3.0 (± 21.25)	8.4 (± 8.02)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-11.5 (± 13.44)	2.0 (± 999999)	7.0 (± 19.80)
Week 100; n=2, 2, 2, 4	-23.0 (± 26.87)	-11.5 (± 17.68)	-2.0 (± 2.83)	8.8 (± 12.04)
Week 112; n=1, 2, 2, 3	-4.0 (± 999999)	-6.0 (± 11.31)	-2.0 (± 4.24)	5.0 (± 13.75)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-4.0 (± 5.66)	4.0 (± 999999)	4.3 (± 9.24)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	2.0 (± 999999)	7.0 (± 25.16)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	15.0 (± 999999)	11.0 (± 26.46)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	23.0 (± 26.87)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-0.5 (± 17.68)	99999 (± 99999)
End of Study; n=4, 2, 2, 5	1.8 (± 10.40)	-6.0 (± 0.00)	5.0 (± 9.90)	3.4 (± 11.76)

Notes:

[29] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[30] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[31] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[32] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Function Tests: ALP at Week 16 and Over Time Through EOS

End point title	Percent Change from Baseline in Liver Function Tests: ALP at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[33]	8[34]	9[35]	14[36]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	-0.5 (± 12.8)	-5.6 (± 8.7)	-17.7 (± 16.0)	5.8 (± 14.7)
Week 16 24 H; n=3, 4, 6, 9	-8.9 (± 6.1)	-1.2 (± 2.8)	-14.8 (± 16.8)	5.9 (± 10.0)
Week 28; n=8, 8, 9, 14	5.5 (± 20.1)	-6.4 (± 9.3)	-10.5 (± 16.1)	1.0 (± 7.2)
Week 40; n=8, 8, 9, 14	2.0 (± 16.9)	-9.3 (± 8.2)	-10.4 (± 14.9)	2.2 (± 10.4)
PDLB at Week 48; n=4, 3, 6, 6	-8.5 (± 13.9)	-0.4 (± 1.5)	-3.3 (± 23.5)	1.7 (± 3.7)
Week 52; n=8, 8, 9, 13	0.1 (± 17.0)	-9.7 (± 11.7)	-4.9 (± 13.5)	2.7 (± 8.3)
Week 64; n=4, 4, 7, 9	-5.6 (± 18.4)	-8.3 (± 10.8)	-0.2 (± 22.5)	3.9 (± 11.0)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	7.1 (± 999999)
Week 76; n=3, 4, 6, 6	-11.2 (± 18.2)	-11.4 (± 13.5)	0.7 (± 18.1)	8.0 (± 13.3)
Week 88; n=3, 2, 5, 5	-12.5 (± 15.9)	-19.6 (± 27.8)	3.2 (± 30.3)	10.6 (± 9.5)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-13.9 (± 15.7)	2.9 (± 999999)	7.6 (± 22.6)
Week 100; n=2, 2, 2, 4	-19.4 (± 19.4)	-13.6 (± 21.2)	-2.5 (± 3.6)	10.1 (± 13.4)
Week 112; n=1, 2, 2, 3	-5.6 (± 999999)	-6.9 (± 13.8)	-2.4 (± 5.5)	5.7 (± 15.6)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-4.8 (± 6.7)	5.8 (± 999999)	4.7 (± 10.5)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	2.9 (± 999999)	6.8 (± 29.3)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	21.7 (± 999999)	11.5 (± 30.8)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	26.0 (± 30.0)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	4.6 (± 26.1)	99999 (± 99999)
End of Study; n=4, 2, 2, 5	7.8 (± 18.2)	-7.2 (± 1.8)	7.1 (± 13.9)	5.3 (± 12.3)

Notes:

[33] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[34] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[35] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[36] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change from Baseline in Liver Function Tests: Gamma Glutamyl Transferase (GGT) at Week 16 and Over Time Through EOS

End point title	Absolute Change from Baseline in Liver Function Tests: Gamma Glutamyl Transferase (GGT) at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[37]	8[38]	9[39]	14[40]
Units: U/L				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	2.8 (± 11.48)	-4.3 (± 5.90)	-9.1 (± 16.06)	7.0 (± 14.88)
Week 16 24 H; n=3, 4, 6, 9	-3.7 (± 16.80)	-4.8 (± 4.35)	-4.3 (± 4.93)	1.1 (± 4.62)
Week 28; n=8, 8, 9, 14	-3.5 (± 11.99)	-5.3 (± 5.57)	-4.1 (± 9.65)	0.6 (± 8.47)
Week 40; n=8, 8, 9, 14	5.3 (± 31.24)	-3.8 (± 9.29)	0.9 (± 16.88)	0.6 (± 7.69)
PDLB at Week 48; n=4, 3, 6, 6	-13.5 (± 23.67)	-5.3 (± 4.16)	-5.3 (± 10.17)	-0.5 (± 10.48)
Week 52; n=8, 8, 9, 13	7.3 (± 36.39)	-4.3 (± 11.13)	6.8 (± 27.79)	1.7 (± 6.64)
Week 64; n=4, 4, 7, 9	-16.0 (± 13.22)	-13.0 (± 14.14)	2.7 (± 19.04)	9.3 (± 22.13)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-3.0 (± 999999)
Week 76; n=3, 4, 6, 6	-20.3 (± 28.36)	-13.3 (± 15.48)	-3.3 (± 11.04)	-0.3 (± 10.19)
Week 88; n=3, 2, 5, 5	-17.0 (± 29.51)	-19.0 (± 25.46)	2.0 (± 7.81)	7.2 (± 4.97)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-25.5 (± 14.85)	5.0 (± 999999)	3.5 (± 0.71)
Week 100; n=2, 2, 2, 4	-25.0 (± 28.28)	-24.5 (± 21.92)	6.5 (± 4.95)	-2.3 (± 14.29)
Week 112; n=1, 2, 2, 3	0.0 (± 999999)	-21.5 (± 9.19)	5.5 (± 4.95)	4.3 (± 10.41)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-50.4 (± 2.6)	8.0 (± 999999)	1.7 (± 9.61)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	7.0 (± 999999)	5.0 (± 7.55)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	10.0 (± 999999)	-0.3 (± 11.59)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	3.0 (± 4.24)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	5.0 (± 4.24)	99999 (± 99999)
End of Study; n=4, 2, 2, 5	22.5 (± 45.68)	-0.5 (± 0.71)	-19.5 (± 27.58)	0.6 (± 5.59)

Notes:

[37] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[38] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[39] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[40] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Function Tests: GGT at Week 16 and Over Time Through EOS

End point title	Percent Change from Baseline in Liver Function Tests: GGT at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[41]	8[42]	9[43]	14[44]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	5.9 (± 18.9)	-9.7 (± 12.7)	-14.8 (± 18.5)	13.9 (± 31.0)
Week 16 24 H; n=3, 4, 6, 9	0.8 (± 32.2)	-9.1 (± 8.6)	-13.2 (± 13.6)	4.7 (± 15.4)
Week 28; n=8, 8, 9, 14	-2.2 (± 21.5)	-12.0 (± 11.7)	-3.2 (± 22.2)	6.8 (± 21.5)
Week 40; n=8, 8, 9, 14	14.4 (± 52.4)	-6.4 (± 18.3)	-1.7 (± 31.6)	7.4 (± 14.4)
PDLB at Week 48; n=4, 3, 6, 6	-8.9 (± 36.3)	-13.3 (± 7.2)	-10.4 (± 30.9)	8.1 (± 17.6)
Week 52; n=8, 8, 9, 13	26.7 (± 69.5)	-3.5 (± 25.1)	6.2 (± 35.2)	5.1 (± 15.3)
Week 64; n=4, 4, 7, 9	-23.0 (± 6.7)	-22.8 (± 17.8)	20.7 (± 69.3)	13.1 (± 24.9)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-6.7 (± 999999)
Week 76; n=3, 4, 6, 6	-22.2 (± 13.6)	-23.1 (± 18.9)	-0.9 (± 38.4)	9.5 (± 13.3)
Week 88; n=3, 2, 5, 5	-13.7 (± 21.1)	-26.8 (± 34.7)	15.6 (± 39.5)	17.9 (± 15.1)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-42.0 (± 11.2)	25.0 (± 999999)	11.9 (± 2.7)
Week 100; n=2, 2, 2, 4	-23.4 (± 11.7)	-38.0 (± 24.8)	33.8 (± 22.9)	6.1 (± 24.2)
Week 112; n=1, 2, 2, 3	0.0 (± 999999)	-36.5 (± 3.4)	28.4 (± 23.5)	16.0 (± 32.9)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-50.4 (± 2.6)	40.0 (± 999999)	8.1 (± 28.7)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	35.0 (± 999999)	18.0 (± 23.4)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	50.0 (± 999999)	2.9 (± 33.3)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	10.0 (± 14.1)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	30.7 (± 32.1)	99999 (± 99999)
End of Study; n=4, 2, 2, 5	39.2 (± 78.5)	-2.2 (± 3.1)	-17.1 (± 24.2)	6.7 (± 18.8)

Notes:

[41] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[42] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[43] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[44] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change from Baseline in Liver Function Tests: Total Bilirubin at

Week 16 and Over Time Through EOS

End point title	Absolute Change from Baseline in Liver Function Tests: Total Bilirubin at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[45]	8[46]	9[47]	14[48]
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	0.079 (± 0.146)	0.098 (± 0.369)	-0.051 (± 0.241)	-0.004 (± 0.208)
Week 16 24 H; n=3, 4, 6, 9	0.060 (± 0.075)	0.163 (± 0.456)	-0.040 (± 0.182)	-0.118 (± 0.105)
Week 28; n=7, 8, 9, 14	0.109 (± 0.149)	0.171 (± 0.470)	0.053 (± 0.230)	0.012 (± 0.272)
Week 40; n=8, 8, 9, 14	0.083 (± 0.115)	0.164 (± 0.437)	0.017 (± 0.092)	0.062 (± 0.434)
PDLB at Week 48; n=4, 3, 6, 6	0.043 (± 0.109)	-0.070 (± 0.594)	0.098 (± 0.252)	-0.085 (± 0.178)
Week 52; n=8, 8, 9, 13	-0.023 (± 0.203)	0.129 (± 0.362)	0.086 (± 0.165)	0.099 (± 0.230)
Week 64; n=4, 4, 7, 9	0.020 (± 0.210)	0.188 (± 0.235)	0.006 (± 0.208)	-0.086 (± 0.188)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-0.420 (± 999999)
Week 76; n=3, 4, 6, 6	0.110 (± 0.105)	0.248 (± 0.357)	-0.043 (± 0.206)	-0.018 (± 0.198)
Week 88; n=3, 2, 5, 5	0.247 (± 0.375)	0.105 (± 0.035)	0.002 (± 0.131)	-0.050 (± 0.131)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	0.020 (± 0.127)	0.170 (± 999999)	0.065 (± 0.035)
Week 100; n=2, 2, 2, 4	-0.040 (± 0.099)	-0.055 (± 0.106)	0.090 (± 0.042)	0.003 (± 0.203)
Week 112; n=1, 2, 2, 3	-0.020 (± 999999)	-0.010 (± 0.269)	0.100 (± 0.141)	-0.060 (± 0.249)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-0.190 (± 0.071)	0.130 (± 999999)	-0.037 (± 0.085)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	0.100 (± 999999)	0.003 (± 0.185)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	0.070 (± 999999)	-0.087 (± 0.199)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-0.090 (± 0.028)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-0.010 (± 0.014)	99999 (± 99999)
End of Study; n=3, 2, 2, 5	0.170 (± 0.123)	0.050 (± 0.113)	0.025 (± 0.205)	0.154 (± 0.082)

Notes:

[45] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[46] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[47] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[48] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Function Tests: Total Bilirubin at Week 16 and Over Time Through EOS

End point title	Percent Change from Baseline in Liver Function Tests: Total Bilirubin at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[49]	8[50]	9[51]	14[52]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 8, 14	19.2 (± 38.5)	15.6 (± 41.7)	3.4 (± 44.1)	1.0 (± 28.0)
Week 16 24 H; n=3, 4, 6, 9	16.4 (± 19.2)	25.3 (± 49.7)	3.1 (± 33.1)	-16.3 (± 12.6)
Week 28; n=7, 8, 9, 14	26.7 (± 36.1)	27.8 (± 51.4)	15.8 (± 36.8)	1.3 (± 37.5)
Week 40; n=8, 8, 9, 14	20.6 (± 27.8)	30.2 (± 51.4)	10.0 (± 21.6)	7.8 (± 46.4)
PDLB at Week 48; n=4, 3, 6, 6	11.8 (± 27.8)	10.8 (± 68.2)	36.5 (± 52.2)	-10.9 (± 29.4)
Week 52; n=8, 8, 9, 13	-8.3 (± 36.6)	27.5 (± 48.8)	25.4 (± 29.4)	15.5 (± 36.4)
Week 64; n=4, 4, 7, 9	10.3 (± 51.0)	28.5 (± 38.0)	10.0 (± 35.7)	-13.3 (± 28.1)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-60.0 (± 999999)
Week 76; n=3, 4, 6, 6	18.1 (± 16.1)	40.1 (± 57.1)	0.3 (± 31.6)	-1.0 (± 33.2)
Week 88; n=3, 2, 5, 5	38.0 (± 53.7)	13.1 (± 1.7)	5.4 (± 29.3)	-7.6 (± 21.4)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	0.8 (± 15.9)	39.5 (± 999999)	9.2 (± 1.7)
Week 100; n=2, 2, 2, 4	-11.9 (± 25.2)	-8.6 (± 15.3)	25.1 (± 4.0)	0.4 (± 31.6)
Week 112; n=1, 2, 2, 3	-5.4 (± 999999)	-5.0 (± 35.1)	37.0 (± 52.4)	-5.8 (± 30.8)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-23.6 (± 3.9)	30.2 (± 999999)	-5.7 (± 12.4)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	23.3 (± 999999)	4.4 (± 25.2)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	16.3 (± 999999)	-7.6 (± 29.7)

Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-13.4 (± 0.9)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-2.9 (± 4.2)	99999 (± 99999)
End of Study; n=3, 2, 2, 5	41.8 (± 36.4)	11.5 (± 26.4)	25.0 (± 69.2)	26.8 (± 16.6)

Notes:

[49] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[50] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[51] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[52] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change from Baseline in Liver Function Tests: Direct Bilirubin at Week 16 and Over Time Through EOS

End point title	Absolute Change from Baseline in Liver Function Tests: Direct Bilirubin at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[53]	8[54]	9[55]	14[56]
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 16; n=8, 7, 7, 12	0.016 (± 0.049)	-0.006 (± 0.095)	0.005 (± 0.094)	0.010 (± 0.061)
Week 16 24 H; n=3, 4, 6, 8	0.013 (± 0.029)	0.055 (± 0.157)	-0.030 (± 0.081)	-0.028 (± 0.041)
Week 28; n=7, 8, 9, 14	0.029 (± 0.055)	0.039 (± 0.140)	0.004 (± 0.062)	0.008 (± 0.073)
Week 40; n=7, 8, 9, 13	0.026 (± 0.050)	0.045 (± 0.160)	-0.005 (± 0.063)	0.020 (± 0.125)
PDLB at Week 48; n=4, 3, 6, 5	-0.005 (± 0.041)	-0.080 (± 0.210)	0.007 (± 0.087)	-0.038 (± 0.065)
Week 52; n=7, 8, 9, 13	-0.024 (± 0.080)	0.034 (± 0.107)	0.015 (± 0.052)	0.031 (± 0.058)
Week 64; n=4, 4, 7, 9	-0.008 (± 0.081)	0.053 (± 0.061)	-0.007 (± 0.076)	-0.019 (± 0.043)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-46.2 (± 999999)
Week 76; n=3, 4, 6, 6	0.027 (± 0.029)	0.098 (± 0.069)	-0.033 (± 0.073)	0.027 (± 0.057)
Week 88; n=3, 2, 5, 5	0.053 (± 0.114)	0.070 (± 0.014)	-0.007 (± 0.043)	0.012 (± 0.026)

PDLB at Week 96; n=0, 1, 1, 2	99999 (± 99999)	0.030 (± 999999)	0.080 (± 999999)	0.045 (± 0.035)
Week 100; n=2, 2, 2, 4	0.000 (± 0.028)	0.010 (± 0.014)	0.050 (± 0.028)	0.018 (± 0.052)
Week 112; n=1, 2, 2, 3	0.020 (± 999999)	0.025 (± 0.049)	0.055 (± 0.035)	0.007 (± 0.061)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-0.040 (± 0.057)	0.070 (± 999999)	0.020 (± 0.035)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	0.030 (± 999999)	0.013 (± 0.046)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	0.050 (± 999999)	-0.003 (± 0.090)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	0.015 (± 0.007)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	0.005 (± 0.007)	99999 (± 99999)
End of Study; n=3, 2, 2, 5	0.050 (± 0.060)	0.010 (± 0.028)	0.028 (± 0.138)	0.053 (± 0.044)

Notes:

[53] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[54] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[55] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[56] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Function Tests: Direct Bilirubin at Week 16 and Over Time Through EOS

End point title	Percent Change from Baseline in Liver Function Tests: Direct Bilirubin at Week 16 and Over Time Through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[57]	8[58]	9[59]	14[60]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 16; n=8, 7, 7, 12	5.9 (± 30.1)	1.5 (± 31.2)	29.1 (± 67.6)	15.1 (± 58.9)
Week 16 24 H; n=3, 4, 6, 8	11.0 (± 16.4)	22.4 (± 50.9)	-0.1 (± 33.0)	-8.8 (± 17.0)
Week 28; n=7, 8, 9, 14	19.0 (± 28.3)	15.4 (± 37.3)	21.2 (± 61.9)	10.1 (± 44.6)
Week 40; n=7, 8, 9, 13	17.9 (± 27.5)	16.7 (± 44.9)	15.5 (± 47.6)	14.3 (± 50.2)
PDLB at Week 48; n=4, 3, 6, 5	2.9 (± 19.5)	-9.9 (± 63.0)	19.3 (± 48.7)	-11.9 (± 23.9)
Week 52; n=7, 8, 9, 13	-12.1 (± 34.3)	17.8 (± 35.1)	25.1 (± 47.0)	19.6 (± 38.5)

Week 64; n=4, 4, 7, 9	4.4 (± 39.7)	18.9 (± 26.7)	8.2 (± 37.3)	-8.6 (± 16.7)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-46.2 (± 999999)
Week 76; n=3, 4, 6, 6	9.9 (± 7.4)	33.4 (± 20.2)	-5.4 (± 30.0)	11.4 (± 21.5)
Week 88; n=3, 2, 5, 5	18.2 (± 35.0)	24.9 (± 14.0)	-3.3 (± 30.3)	5.6 (± 12.1)
PDLB at Week 96; n=0, 1, 1, 2	99999 (± 99999)	7.5 (± 999999)	53.3 (± 999999)	17.1 (± 10.0)
Week 100; n=2, 2, 2, 4	-3.8 (± 16.3)	4.3 (± 6.1)	37.0 (± 13.7)	7.5 (± 23.2)
Week 112; n=1, 2, 2, 3	15.4 (± 999999)	5.3 (± 13.7)	46.4 (± 37.3)	4.1 (± 22.5)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-10.0 (± 14.1)	46.7 (± 999999)	7.7 (± 13.3)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	20.0 (± 999999)	7.2 (± 18.3)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	33.3 (± 999999)	3.4 (± 38.5)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	6.7 (± 4.6)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	2.4 (± 3.4)	99999 (± 99999)
End of Study; n=3, 2, 2, 5	34.3 (± 45.6)	5.4 (± 14.7)	96.1 (± 185.5)	40.8 (± 46.7)

Notes:

[57] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[58] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[59] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

[60] - 99999=0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change from Baseline in Liver Function Tests: Prothrombin International Normalized Ratio at Week 16 and over time through EOS

End point title	Absolute Change from Baseline in Liver Function Tests: Prothrombin International Normalized Ratio at Week 16 and over time through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[61]	8[62]	9[63]	14[64]
Units: ratio				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 9, 14	-0.012 (± 0.054)	-0.006 (± 0.093)	0.011 (± 0.068)	0.055 (± 0.180)

Week 16 24 H; n=3, 4, 7, 9	0.047 (± 0.111)	-0.085 (± 0.093)	-0.017 (± 0.117)	0.036 (± 0.104)
Week 28; n=8, 8, 8, 14	-0.054 (± 0.148)	-0.059 (± 0.109)	-0.040 (± 0.107)	-0.014 (± 0.167)
Week 40; n=8, 8, 9, 14	-0.021 (± 0.113)	-0.024 (± 0.099)	-0.022 (± 0.125)	0.034 (± 0.143)
PDLB at Week 48; n=4, 3, 6, 6	-0.038 (± 0.054)	-0.067 (± 0.150)	-0.023 (± 0.121)	0.022 (± 0.048)
Week 52; n=7, 8, 9, 14	-0.094 (± 0.139)	-0.053 (± 0.057)	-0.034 (± 0.076)	-0.002 (± 0.076)
Week 64; n=4, 3, 7, 9	-0.038 (± 0.089)	-0.100 (± 0.082)	-0.043 (± 0.130)	0.012 (± 0.055)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	0.040 (± 999999)
Week 76; n=3, 4, 6, 6	-0.033 (± 0.049)	-0.110 (± 0.130)	-0.065 (± 0.136)	0.020 (± 0.046)
Week 88; n=3, 2, 5, 5	-0.053 (± 0.040)	-0.225 (± 0.177)	-0.004 (± 0.083)	0.038 (± 0.026)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-0.195 (± 0.134)	0.090 (± 999999)	0.045 (± 0.078)
Week 100; n=2, 2, 2, 4	0.000 (± 0.014)	-0.225 (± 0.163)	-0.020 (± 0.099)	0.063 (± 0.045)
Week 112; n=1, 2, 2, 3	0.050 (± 999999)	-0.240 (± 0.184)	0.035 (± 0.078)	0.047 (± 0.083)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-0.175 (± 0.247)	0.050 (± 999999)	0.053 (± 0.021)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	0.070 (± 999999)	0.043 (± 0.032)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	0.080 (± 999999)	0.040 (± 0.026)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	0.070 (± 0.042)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	0.045 (± 0.092)	99999 (± 99999)
End of Study; n=4, 2, 2, 5	-0.115 (± 0.170)	-0.045 (± 0.049)	-0.035 (± 0.021)	-0.106 (± 0.149)

Notes:

[61] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[62] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[63] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[64] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Liver Function Tests: Prothrombin International Normalized Ratio at Week 16 and over time through EOS

End point title	Percent Change from Baseline in Liver Function Tests: Prothrombin International Normalized Ratio at Week 16 and over time through EOS

End point description:

PDLB=post-dose liver biopsy

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 16, Week 16 + 24 hours (H), Weeks 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[65]	8[66]	9[67]	14[68]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 16; n=9, 8, 9, 14	-1.0 (± 4.8)	-0.7 (± 7.7)	1.2 (± 6.4)	2.6 (± 8.6)
Week 16 24 H; n=3, 4, 7, 9	4.4 (± 10.3)	-7.0 (± 6.9)	-1.0 (± 10.2)	3.5 (± 9.9)
Week 28; n=8, 8, 8, 14	-3.9 (± 11.8)	-4.9 (± 8.5)	-3.3 (± 9.1)	1.2 (± 8.7)
Week 40; n=8, 8, 9, 14	-1.2 (± 9.6)	-1.6 (± 7.8)	-1.6 (± 11.3)	3.7 (± 13.0)
PDLB at Week 48; n=4, 3, 6, 6	-3.2 (± 4.7)	-5.5 (± 13.3)	-1.5 (± 10.3)	2.2 (± 4.8)
Week 52; n=7, 8, 9, 14	-7.7 (± 10.2)	-4.7 (± 4.9)	-2.9 (± 6.3)	0.3 (± 6.9)
Week 64; n=4, 3, 7, 9	-3.2 (± 7.9)	-8.4 (± 7.1)	-3.2 (± 11.4)	1.3 (± 5.3)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	3.9 (± 999999)
Week 76; n=3, 4, 6, 6	-2.8 (± 4.0)	-8.8 (± 9.9)	-5.3 (± 11.8)	2.0 (± 4.6)
Week 88; n=3, 2, 5, 5	-4.7 (± 3.1)	-17.9 (± 12.5)	-0.3 (± 8.0)	3.7 (± 2.4)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-15.6 (± 9.2)	9.0 (± 999999)	4.6 (± 7.8)
Week 100; n=2, 2, 2, 4	0.0 (± 1.4)	-18.0 (± 11.3)	-1.8 (± 9.6)	6.2 (± 4.5)
Week 112; n=1, 2, 2, 3	4.9 (± 999999)	-19.1 (± 12.9)	3.5 (± 7.7)	4.7 (± 8.4)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-13.4 (± 18.9)	5.0 (± 999999)	5.3 (± 2.1)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	7.0 (± 999999)	4.3 (± 3.3)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	8.0 (± 999999)	3.9 (± 2.5)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	7.0 (± 4.3)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	4.8 (± 9.4)	99999 (± 99999)
End of Study; n=4, 2, 2, 5	-9.1 (± 12.7)	-4.3 (± 4.9)	-3.6 (± 2.0)	-5.8 (± 4.7)

Notes:

[65] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[66] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[67] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[68] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Serum Z-AAT Over Time through EOS

End point title	Absolute Change in Serum Z-AAT Over Time through EOS

End point description:

PDLB=post-dose liver biopsy
Full Analysis Set: All randomized 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, Weeks 2, 4, 6, 16, 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[69]	8[70]	9[71]	14[72]
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 2; n=9, 7, 9, 14	-125.511 (± 59.955)	-156.714 (± 58.127)	-169.044 (± 40.328)	16.929 (± 37.723)
Week 4; n=9, 8, 9, 14	-146.267 (± 68.511)	-178.413 (± 58.821)	-181.389 (± 41.857)	-0.429 (± 18.826)
Week 6; n=9, 8, 9, 14	-176.100 (± 47.242)	-192.719 (± 65.087)	-188.781 (± 43.539)	7.000 (± 26.712)
Week 16; n=8, 8, 9, 14	-158.650 (± 50.266)	-185.213 (± 58.059)	-182.240 (± 45.710)	10.286 (± 29.374)
Week 28; n=8, 8, 9, 14	-123.288 (± 62.112)	-174.275 (± 57.293)	-175.136 (± 52.838)	-0.500 (± 25.035)
Week 40; n=8, 8, 9, 14	-122.288 (± 70.057)	-165.763 (± 59.312)	-164.629 (± 63.830)	1.429 (± 20.137)
PDLB at Week 48; n=4, 3, 6, 6	-189.850 (± 64.556)	-150.900 (± 17.521)	-194.535 (± 51.128)	14.333 (± 38.754)
Week 52; n=8, 8, 9, 14	-116.188 (± 72.983)	-157.300 (± 56.023)	-165.741 (± 64.535)	-13.643 (± 36.527)
Week 64; n=4, 4, 7, 9	-187.325 (± 94.397)	-191.150 (± 80.589)	-190.284 (± 45.070)	0.333 (± 27.208)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-6.00 (± 999999)
Week 76; n=3, 4, 6, 6	-164.067 (± 65.875)	-189.225 (± 91.259)	-177.060 (± 49.718)	-9.500 (± 20.907)
Week 88; n=3, 2, 5, 5	-142.767 (± 89.632)	-260.200 (± 82.166)	-186.116 (± 44.539)	-1.800 (± 28.490)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 999999)	-271.100 (± 90.793)	-194.160 (± 999999)	-35.000 (± 15.556)
Week 100; n=2, 2, 2, 4	-204.650 (± 18.597)	-244.100 (± 91.358)	-187.650 (± 3.323)	-60.725 (± 84.824)
Week 112; n=1, 2, 2, 3	-233.000 (± 999999)	-263.100 (± 91.358)	-182.550 (± 3.182)	-22.333 (± 22.679)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-237.650 (± 102.743)	-183.000 (± 999999)	-26.000 (± 22.271)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	-183.300 (± 999999)	-8.000 (± 22.650)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	-89.1 (± 999999)	9.333 (± 11.719)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	7.500 (± 9.192)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-192.240 (± 81.657)	99999 (± 99999)
End of Study; n=4, 3, 2, 4	-42.750 (± 7.089)	-103.533 (± 3.443)	-39.000 (± 1.414)	19.750 (± 30.966)

Notes:

[69] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[70] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[71] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[72] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Serum Z-AAT Over Time through EOS

End point title	Percent Change in Serum Z-AAT Over Time through EOS

End point description:

PDLB=post-dose liver biopsy
Full Analysis Set: All randomized 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, Weeks 2, 4, 6, 16, 28, 40, 48, 52, 64, 72, 76, 88, 96, 100, 112, 124, 136, 148, 160, Early Termination, EOS

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[73]	8[74]	9[75]	14[76]
Units: percentage change				
arithmetic mean (standard deviation)				
Week 2; n=9, 7, 9, 14	-50.8 (± 21.9)	-69.9 (± 11.4)	-85.5 (± 4.8)	10.0 (± 23.8)
Week 4; n=9, 8, 9, 14	-60.0 (± 24.6)	-82.2 (± 7.1)	-91.8 (± 2.5)	0.5 (± 8.7)
Week 6; n=9, 8, 9, 14	-71.9 (± 14.0)	-88.4 (± 5.0)	-95.5 (± 1.9)	3.4 (± 11.4)
Week 16; n=8, 8, 9, 14	-62.4 (± 17.0)	-85.7 (± 7.6)	-91.9 (± 5.8)	4.3 (± 12.2)
Week 28; n=8, 8, 9, 14	-48.2 (± 20.6)	-80.6 (± 7.9)	-87.6 (± 10.4)	0.1 (± 11.2)
Week 40; n=8, 8, 9, 14	-48.3 (± 23.4)	-76.5 (± 10.5)	-81.3 (± 18.8)	0.3 (± 9.2)
PDLB at Week 48; n=4, 3, 6, 6	-73.9 (± 16.7)	-89.2 (± 2.5)	-93.9 (± 5.0)	8.7 (± 19.0)
Week 52; n=8, 8, 9, 14	-45.9 (± 24.7)	-73.0 (± 12.9)	-82.1 (± 20.5)	-5.3 (± 14.9)
Week 64; n=4, 4, 7, 9	-70.1 (± 23.5)	-77.6 (± 9.5)	-92.2 (± 5.7)	2.1 (± 12.3)
PDLB at Week 72; n=0, 0, 0, 1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-2.4 (± 999999)
Week 76; n=3, 4, 6, 6	-71.8 (± 19.6)	-75.1 (± 9.0)	-88.8 (± 10.1)	-2.4 (± 9.3)
Week 88; n=3, 2, 5, 5	-60.1 (± 32.6)	-77.8 (± 7.2)	-90.3 (± 6.3)	0.5 (± 11.4)
PDLB at Week 96; n=0, 2, 1, 2	99999 (± 99999)	-80.9 (± 9.1)	-95.6 (± 999999)	-11.7 (± 4.2)
Week 100; n=2, 2, 2, 4	-82.5 (± 10.1)	-72.5 (± 11.2)	-93.8 (± 0.3)	-21.3 (± 29.6)
Week 112; n=1, 2, 2, 3	-91.7 (± 999999)	-78.4 (± 9.9)	-91.3 (± 3.5)	-8.4 (± 9.2)
Week 124; n=0, 2, 1, 3	99999 (± 99999)	-70.1 (± 15.2)	-90.1 (± 999999)	-9.9 (± 9.1)
Week 136; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	-90.3 (± 999999)	-3.2 (± 8.8)
Week 148; n=0, 0, 1, 3	99999 (± 99999)	99999 (± 99999)	-89.1 (± 999999)	3.1 (± 4.1)
Week 160; n=0, 0, 0, 2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	2.4 (± 2.9)
Early Termination; n=0, 0, 2, 0	99999 (± 99999)	99999 (± 99999)	-91.7 (± 8.5)	99999 (± 99999)
End of Study; n=4, 3, 2, 4	-18.0 (± 2.7)	-53.8 (± 6.6)	-23.4 (± 0.1)	9.1 (± 12.4)

Notes:

[73] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[74] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[75] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

[76] - 0 participants analyzed; 999999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): ARO-AAT Plasma Concentration Summary for the Double-Blind Phase

End point title	Pharmacokinetics (PK): ARO-AAT Plasma Concentration Summary for the Double-Blind Phase

End point description:

PK Population: all Full Analysis Set participants who have at least 1 measurable plasma concentration data

End point type	Secondary

End point timeframe:

Fazirsiran participants without fibrosis: Pre-dose, 1 hour, 2 hour, 24 hours post-dose on Day 1 (+/- 1 day). Fazirsiran participants with fibrosis: Pre-dose, 1 hour, 2 hours, 24 hours post-dose on Day 1 and Week 16
(+/- 1 day).

End point values	Fazirsiran 25 mg: Participants With No Fibrosis	Fazirsiran 25 mg: Participants With Fibrosis	Fazirsiran 100 mg: Participants With No Fibrosis	Fazirsiran 100 mg: Participants With Fibrosis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[77]	4	3[78]	5
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1, Pre-Dose; n=4, 4, 3, 5, 2, 7	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Day 1, 1 h; n=4, 4, 3, 5, 2, 7	29.9 (± 75.6)	50.6 (± 66.8)	190 (± 17.9)	173 (± 25.7)
Day 1, 2h; n=4, 4, 3, 5, 2, 7	35.0 (± 83.0)	60.7 (± 72.5)	208 (± 11.6)	199 (± 32.2)
Day 1, 24h; n=4, 4, 3, 5, 2, 6	9.92 (± 99.6)	6.33 (± 176)	69.0 (± 88.4)	26.6 (± 59.1)
Week 16, Pre-Dose; n=1, 4, 3, 5, 1, 7	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Week 16, 1h; n=NA, 3, NA, 5, NA, 7	99999 (± 99999)	38.1 (± 75.3)	99999 (± 99999)	38.1 (± 75.3)
Week 16, 2h; n=NA, 3, NA, 5, NA, 7	99999 (± 99999)	45.1 (± 70.1)	99999 (± 99999)	45.1 (± 70.1)
Week 16, 24h; n=NA, 3, NA, 5, NA, 7	99999 (± 99999)	3.64 (± 123)	99999 (± 99999)	3.64 (± 123)

Notes:

[77] - 99999=NA (not applicable): data not collected at this time point per protocol

[78] - 99999=NA (not applicable): data not collected at this time point per protocol

End point values	Fazirsiran 200 mg: Participants With No	Fazirsiran 200 mg: Participants With Fibrosis		

	Fibrosis			
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2[79]	7[80]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1, Pre-Dose; n=4, 4, 3, 5, 2, 7	0 (± 0)	0 (± 0)		
Day 1, 1 h; n=4, 4, 3, 5, 2, 7	495 (± 71.8)	356 (± 75.9)		
Day 1, 2h; n=4, 4, 3, 5, 2, 7	537 (± 81.9)	471 (± 56.5)		
Day 1, 24h; n=4, 4, 3, 5, 2, 6	11.7 (± 17100)	27.7 (± 612)		
Week 16, Pre-Dose; n=1, 4, 3, 5, 1, 7	0 (± 0)	0 (± 0)		
Week 16, 1h; n=NA, 3, NA, 5, NA, 7	99999 (± 99999)	396 (± 64.9)		
Week 16, 2h; n=NA, 3, NA, 5, NA, 7	99999 (± 99999)	487 (± 62.5)		
Week 16, 24h; n=NA, 3, NA, 5, NA, 7	99999 (± 99999)	104 (± 26.2)		

Notes:

[79] - 99999=NA (not applicable): data not collected at this time point per protocol

[80] - 99999=NA (not applicable): data not collected at this time point per protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Positive for Anti-Drug Antibodies to Fazirsiran

End point title	Number of Participants Positive for Anti-Drug Antibodies to Fazirsiran[81]

End point description:

PDLB=post-dose liver biopsy
Safety Analysis Set: all participants who received at least one dose of fazirsiran; n=number of participants with an assessment at given time point

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 16, 28, 40, 48, 52, 64, 76, 88, 96, 100, 112, 124, 136, 148 or Early Termination

Notes:

[81] - 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: Per protocol, the placebo arm was not included in the analysis set.

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	9	
Units: participants				
Baseline; n=9, 8, 9	0	2	2	
Week 4; n=9, 8, 9	0	1	2	
Week 16; n=7, 8, 9	0	1	2	
Week 28; n=7, 8, 8	0	2	1	
Week 40; n=8, 8, 9	0	2	2	
PDLB at Week 48; n=1, 0, 1	0	0	0	
Week 52; n=6, 5, 7	0	1	0	
Week 64; n=4, 4, 7	0	0	0	
Week 76; 3, 4, 6	0	1	0	

Week 88; n=3, 2, 5	0	0	0	
PDLB at Week 96; n=0, 0, 1	0	0	0	
Week 100; n=2, 2, 2	0	0	0	
Week 112; n=1, 2, 2	0	0	1	
Week 124; n=0, 2, 1	0	0	1	
Week 136; 0, 0, 1	0	0	1	
Week 148; n=0, 0, 1	0	0	1	
Early Termination; n=0, 0, 2	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Shifts From Baseline in Metavir Fibrosis Stage at Post-Dose Biopsy for Participants with Fibrosis

End point title	Percentage of Participants With Shifts From Baseline in Metavir Fibrosis Stage at Post-Dose Biopsy for Participants with Fibrosis

End point description:

The METAVIR scoring system is a system used to assess the extent of inflammation and fibrosis by histopathological evaluation in a liver biopsy. The stage represents the amount of fibrosis or scarring: 0= no fibrosis; 1=portal fibrosis without septa; 2=portal fibrosis with few septa; 3=numerous septa without cirrhosis; 4=cirrhosis.

Biopsy Analysis Set: All randomized participants who received at least one dose of study drug and had at least one central read histology biopsy result. n=participants eligible to meet the defined criteria. (For example, participants with baseline Metavir fibrosis score 0 are not eligible for improvement; participants with baseline Metavir fibrosis score 4 are not eligible for worsening.)

End point type	Secondary

End point timeframe:

Baseline, Post-dose at Weeks 48 (+/- 2 weeks) or Week 72 (+/- 4 weeks) or Week 96 (+/- 4 weeks)

End point values	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	7	9
Units: percentage of participants				
number (not applicable)				
>= 1-point improvement from baseline; n=3, 5, 6, 8	66.7	40.0	50.0	37.5
no change from baseline; n=4, 5, 7, 9	25.0	60.0	14.3	44.4
>= 1-point worsening from baseline; n=1, 3, 6, 4	25.0	0.0	42.9	22.2

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Participants without fibrosis: up to 72 weeks.
Participants with evidence of fibrosis: up to 216 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Fazirsiran 25 mg

Reporting group description:

Participants with no fibrosis: Fazirsiran 25 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 25 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Fazirsiran 100 mg

Reporting group description:

Participants with no fibrosis: Fazirsiran 100 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 100 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Fazirsiran 200 mg

Reporting group description:

Participants with no fibrosis: Fazirsiran 200 mg administered on Day 1 and Week 4.

Participants with fibrosis: Fazirsiran 200 mg administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Placebo

Reporting group description:

Participants with no fibrosis: Placebo administered on Day 1 and Week 4.

Participants with fibrosis: Placebo administered on Day 1, Week 4, and Week 16, then every 12 weeks up to 18 total doses.

Reporting group title	Fazirsiran 25 mg DB/200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 25 mg and completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Reporting group title	Fazirsiran 100 mg DB/200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 100 mg and completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Reporting group title	Fazirsiran 200 mg DB/200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) fazirsiran 200 mg and completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Reporting group title	Placebo DB/Fazirsiran 200 mg OL

Reporting group description:

Participants with fibrosis at Screening who received double-blind (DB) placebo and completed the post-dose liver biopsy at Week 48 (or Week 72 or Week 96) entered the open-label phase and received fazirsiran 200 mg every 12 weeks for the duration of the study.

Serious adverse events	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	2 / 9 (22.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo	Fazirsiran 25 mg DB/200 mg OL	Fazirsiran 100 mg DB/200 mg OL
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 14 (21.43%)	1 / 4 (25.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Presyncope			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (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
Pulmonary haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (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
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			

subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Fazirsiran 200 mg DB/200 mg OL	Placebo DB/Fazirsiran 200 mg OL	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	1 / 9 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	8 / 8 (100.00%)	9 / 9 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Poor venous access			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Withdrawal hypertension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	1	5	0
Injection site erythema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			

subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Injection site reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	9
Chills			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Injection site pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Cyst			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Medical device site haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Medical device site pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pain			

subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Atypical mycobacterial pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Prostatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Cough			
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Breathing-related sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Bronchiectasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lung disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pulmonary mass			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Upper-airway cough syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Post-traumatic stress disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Forced expiratory volume decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Blood creatine phosphokinase			

increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Crystal urine present			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Forced vital capacity decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lung diffusion test decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Spirometry abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Concussion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Injection site erythema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	2 / 9 (22.22%)	2 / 8 (25.00%)	3 / 9 (33.33%)
occurrences (all)	2	2	5
Vaccination complication			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Injection site rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Muscle contusion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Muscle strain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Post procedural contusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Post procedural haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Post procedural pruritus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Procedural dizziness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Vascular access site bruising			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Hamartoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Coronary artery disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Left atrial enlargement			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 9 (44.44%)	1 / 8 (12.50%)	2 / 9 (22.22%)
occurrences (all)	4	1	3
Dizziness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Facial paralysis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Migraine			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Sinus headache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Urinary incontinence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lymph node pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Eyelid ptosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	2 / 9 (22.22%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	2	1	0

Abdominal pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Inguinal hernia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Abdominal distension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Abdominal rigidity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Diverticulum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0

Haematochezia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oesophageal ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pancreatic steatosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pancreatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rectal prolapse			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hepatic steatosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Rash maculo-papular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Basal cell carcinoma			

subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Blood blister			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Rosacea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Skin laceration			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Nephrolithiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Urge incontinence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Arthralgia			
subjects affected / exposed	2 / 9 (22.22%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Back pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	2 / 9 (22.22%)
occurrences (all)	1	1	2
Neck pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	2
Pain in extremity			

subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Musculoskeletal discomfort			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Bursitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rhabdomyolysis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Acrochordon			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	7 / 9 (77.78%)
occurrences (all)	0	2	7
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Body tinea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Dermatophytosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dermatophytosis of nail			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Folliculitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Periorbital cellulitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Incision site cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Norovirus infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pertussis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Wound infection staphylococcal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Vitamin B complex deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Vitamin B12 deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo	Fazirsiran 25 mg DB/200 mg OL	Fazirsiran 100 mg DB/200 mg OL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	4 / 4 (100.00%)	4 / 5 (80.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			

Flushing			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 14 (14.29%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Poor venous access			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Withdrawal hypertension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 14 (14.29%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	2	2	1
Injection site erythema			
subjects affected / exposed	2 / 14 (14.29%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Injection site reaction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Chest discomfort			

subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cyst			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Medical device site haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Medical device site pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Atypical mycobacterial pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			

Abnormal uterine bleeding			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Prostatitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 14 (21.43%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Respiratory tract congestion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Breathing-related sleep disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Bronchial hyperreactivity			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Bronchiectasis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lung disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pleuritic pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pulmonary mass			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Confusional state			

subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Post-traumatic stress disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Forced expiratory volume decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Crystal urine present			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Forced vital capacity decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lung diffusion test decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Prothrombin time prolonged			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Spirometry abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injection site induration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injection site pain			

subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Procedural pain			
subjects affected / exposed	3 / 14 (21.43%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Vaccination complication			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injection site rash			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Post procedural contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Post procedural haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Post procedural pruritus			

subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Procedural dizziness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vascular access site bruising			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Hamartoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Coronary artery disease			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Left atrial enlargement			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Supraventricular tachycardia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	4	0	2
Dizziness			

subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Dysgeusia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Facial paralysis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sinus headache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Somnolence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lymph node pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Lymphopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eyelid ptosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 14 (21.43%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	3	0	2
Diarrhoea			
subjects affected / exposed	2 / 14 (14.29%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			

subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal rigidity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diverticulum			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oesophageal ulcer			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pancreatic steatosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Rectal prolapse			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hepatic steatosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 14 (21.43%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Alopecia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood blister			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rosacea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Dysuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urge incontinence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	3 / 14 (21.43%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle strain			

subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rhabdomyolysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Acrochordon			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 14 (14.29%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	2
Body tinea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Cellulitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dermatophytosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dermatophytosis of nail			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diverticulitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			
subjects affected / exposed	3 / 14 (21.43%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Periorbital cellulitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Incision site cellulitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Norovirus infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pertussis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Wound infection staphylococcal			

subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitamin B complex deficiency			
subjects affected / exposed	0 / 14 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitamin B12 deficiency			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	1 / 14 (7.14%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Fazirsiran 200 mg DB/200 mg OL	Placebo DB/Fazirsiran 200 mg OL	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	9 / 9 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Poor venous access			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Withdrawal hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injection site reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Chest discomfort			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Cyst			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Flank pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Medical device site haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Medical device site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Atypical mycobacterial pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Prostatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Cough				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Dyspnoea exertional				
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)		
occurrences (all)	0	2		
Oropharyngeal pain				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Respiratory tract congestion				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Rhinorrhoea				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Breathing-related sleep disorder				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Bronchial hyperreactivity				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Bronchiectasis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)		
occurrences (all)	0	1		
Lung disorder				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Nasal congestion				

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pleuritic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pulmonary mass			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Throat irritation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Post-traumatic stress disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Investigations			

Glomerular filtration rate decreased				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Activated partial thromboplastin time prolonged				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Blood bilirubin increased				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Urine analysis abnormal				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Forced expiratory volume decreased				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
C-reactive protein increased				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Crystal urine present				
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)		
occurrences (all)	0	1		
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Forced vital capacity decreased				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
International normalised ratio increased				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Lung diffusion test decreased				

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Prothrombin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Spirometry abnormal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injection site induration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vaccination complication			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Contusion			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Head injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injection site rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ligament sprain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Muscle contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Post procedural contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Post procedural pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Procedural dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vascular access site bruising			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Wound			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Congenital, familial and genetic disorders			
Hamartoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Coronary artery disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Left atrial enlargement			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Facial paralysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sinus headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Urinary incontinence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lymph node pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Eyelid ptosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Inguinal hernia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Abdominal distension			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Abdominal pain lower			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Abdominal rigidity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Diverticulum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Haematochezia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oesophageal ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pancreatic steatosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pancreatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rectal prolapse			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Toothache			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hepatic steatosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Basal cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Blood blister			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dermatitis contact			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hyperhidrosis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Night sweats			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Petechiae			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash erythematous			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rosacea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Skin laceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nephrolithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Urge incontinence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Bursitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Osteoarthritis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rhabdomyolysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Acrochordon			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 5 (20.00%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Body tinea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Candida infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dermatophytosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Dermatophytosis of nail				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Diverticulitis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Escherichia urinary tract infection				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Folliculitis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Gastroenteritis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Gastroenteritis viral				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Gingivitis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Upper respiratory tract infection				
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)		
occurrences (all)	2	0		
Urinary tract infection				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Periorbital cellulitis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Incision site cellulitis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)		
occurrences (all)	0	0		
Infective exacerbation of bronchiectasis				

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Norovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pertussis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Viral infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	
Vitamin B complex deficiency subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2019	The protocol was amended in response to recommendations based on review by the U.S. Food and Drug Administration. Correction of administrative, grammatical, formatting errors and inconsistencies; rewording for clarity. 1. Protocol Synopsis: Section regarding Number of Doses edited to clarity the minimum number of doses to be administered to Part A and Part B study patients. 2. Protocol Synopsis: Section regarding Study Assessments edited to clarify that FibroScan evaluation will performed, where available. This clarification was carried throughout the document. 3. Protocol Synopsis: Treatment Stopping and Study Modification Rules - #2 edited to state that evaluation and ARO-AAT study modification/discontinuation rules for elevated ALTs or worsening hepatic function (i.e., cirrhosis) are provided in Appendix 3. - Additional language added as follows: Any discontinued patient will be followed with appropriate assessments and monitoring (either per schedule of assessments [SOA] or with more intensive evaluation) through end-of-study. 4. The Schedule of Assessments table was edited for clarity, including: - Plasma Z-AAT has been changed to Z-AAT Level. Serum will be obtained. - APRI measurement schedule defined. 5. DSMB Stopping Rules: - #2 edited to state that evaluation and ARO-AAT study modification/discontinuation rules for elevated ALTs or worsening hepatic function (i.e., cirrhosis) are provided in Appendix 3. - Additional language added as follows: Any discontinued patient will be followed with appropriate assessments and monitoring (either per SOA or with more intensive evaluation) through end-of-study. 6. Exclusion Criteria: - Exclusion Criteria #4 was changed from Creatinine > 1.3 mg/dL to estimated glomerular filtration rate (eGFR) < 60 mL/min at Screening (one retest permitted).
15 April 2019	(continued) 7. Overview of Procedures: - Part A doses: All Part A patients will continue to receive their allocated Part A dose level for at least 3 doses with continued dose administration every 84 days after the third dose until the Part B dose is chosen. Thus, a subject in Part A will receive a minimum of three Part A doses while the maximum number of doses will depend on enrollment rates and timing of initiation of part B. - Part B Doses: In Part B of the study, all patients from Part A will rollover to receive a single dose level. of ARO-AAT (or volume matched placebo) for an additional 6 approximately quarterly (Q84 days) doses. After Part B is open, any newly enrolled patients will receive at least 9 doses at the Part B dose level. Thus, subjects in Part B will receive six to nine Part B doses, depending on when they were enrolled. 8. Clinical Laboratory Tests: - Under Biochemistry, creatinine clearance was removed and replaced with eGFR. 9. Study Formulation Administration: The following text was added to the first paragraph of Section 9.5: There will be no patient self-administration in this study.

15 April 2019	(continued) 10. Appendix 3: -Title of Appendix 3 changed, as follows: ELEVATED ALT OR WORSENING HEPATIC FUNCTION STUDY MODIFICATION AND PATIENT DISCONTINUATION RULES - The following stopping rule was added: o APRI (using 40 U/L as ULN) will be calculated per SOA at baseline, Day 113, then approximately every 168 days (or earlier if development of cirrhosis is suspected clinically). Any increase from baseline to an APRI value > 2.0 (must be confirmed on repeat) will trigger liver biopsy. For patients with baseline APRI > 2.0 but who are eligible based on pre-dose biopsy, AST to Platelet Ratio Index (APRI) will be calculated per SOA and a ≥ 50% increase from baseline (must be confirmed on repeat) will trigger liver biopsy. o Investigator may elect to confirm an elevated APRI as a biomarker of cirrhosis with magnetic resonance elastography (MRE) if available PRIOR to proceeding to biopsy. If MRE is NOT consistent with cirrhosis then biopsy is not indicated and the patient may stay on study. Alternatively, investigator may elect to proceed directly from APRI to biopsy. o If cirrhosis (F4 or equivalent) is detected on liver biopsy the patient will be discontinued from treatment and followed through EOS per SOA. This biopsy will represent EOS biopsy for purposes of end-point determination. If cirrhosis is not confirmed on liver biopsy, patient may continue on treatment. 11. Appendix 4 Declining Platelet Study Modification and Patient Discontinuation Rules: The following was added to Appendix 4: - Any confirmed reduction in platelets (<150,000) associated with clinically related symptoms (e.g., increased bruising, bleeding, petechiae) will warrant discontinuation of study treatment. - confirmed reduction in platelets (<150,000) associated with a clinical diagnosis of portal hypertension (based on clinical signs and symptoms) will warrant discontinuation of study treatment.
28 April 2020	Protocol Amendment Version 3.0 updates the primary objective for Part A, removes the need for Part A day 113 liver biopsy, allows patients without fibrosis (F0) to participate in Part A only, and allows patients with F1 to participate in Parts A and B of the study. It incorporates protocol modifications due to these major changes, contains general edits to improve document clarity, and harmonizes multiple country-specific revisions. 1. The primary objective of Part A, which is to select a dose for Part B, will be based on safety and percent change in serum Z-AAT over time from baseline to Day 113 after treatment with ARO-AAT compared to placebo. 2. The study will allow patients with biopsy-confirmed fibrosis scores of F1-F3 (or equivalent) to participate in Part A and B of the study. Patients with no fibrosis (F0) may only participate in Part A. Prior biopsy results are allowable depending on the scenarios described for diagnosis of fibrosis stage for inclusion/exclusion purposes only. All patients with intent to continue into Part B will require a baseline biopsy conducted as part of the study. 3. Removal of D113 liver biopsy in Part A. 4. A subject with no fibrosis who participates in Part A and is not eligible for Part B will be followed quarterly for AAT levels and pulmonary safety for approximately 1 year after their last dose. 5. To allow biopsy-confirmed Metavir F1 to F3 (or equivalent fibrosis grading scale) to participate in AROAAT2001 study.

18 December 2020	Protocol Amendment Version 4.0 reflects a change to the AROAAT2001 study design. The Phase 2/3 adaptive design has been modified to remove the Phase 3 portion (Part B) and focus the study on Phase 2 only. The primary objective has been revised as a result of the revised study design and the primary endpoint for Part A has become the primary endpoint for the revised study. It incorporates protocol modifications to align with the study design change and contains general edits to improve document clarity. 1. The primary objective of the study has been revised to select a dose level for use in later stage development based on a combined evaluation of safety and pharmacodynamic effects of ARO-AAT. 2. Number of subjects reduced from 120 to approximately 36 (maintains Part A size). 3. Post-dose biopsy will be collected at Week 48 for subjects with fibrosis at screening (Week 72 or 96 for subjects already beyond Week 48 at the time of Institutional Review Board/Ethics Committee (IRB/EC) approval of protocol version 4.0). 4. Open-Label Phase – following the post-dose biopsy, patients can continue to receive ARO-AAT at the selected dose level for the duration of the study.
11 November 2021	The Global Protocol has been amended to: a. Extend the q12 week dosing duration for fibrosis patients. b. Include incidence of anti-drug antibodies (ADA) to ARO-AAT as a secondary endpoint. c. Reclassify Metavir fibrosis stage from an exploratory endpoint to a secondary endpoint. d. Provide editorial clarification. 1. For patients with fibrosis, the duration of the study is up to 216 weeks, with an 8-week Screening period, a 196 week study dosing period, followed by a Study Completion visit performed within 4-12 weeks from the dosing visit. 2. Incidence of anti-drug antibodies to ARO-AAT was added as a secondary endpoint. 3. Change from baseline in Metavir fibrosis stage at post-dose biopsy was reclassified from an exploratory endpoint to a secondary endpoint and Metavir fibrosis score was changed to Metavir fibrosis stage.

29 August 2022	1. This global protocol has been amended to inform of fazirsiran dose selection by the Sponsor based on review of cumulative safety, efficacy, and pharmacodynamic (PD) data from the fazirsiran clinical program (clinical studies AROAAT1001, AROAAT2001, and AROAAT2002). The amendment specifies that all subjects who are ongoing after dose selection will receive the selected fazirsiran dose (200 mg) in the open-label phase for the duration of the study. 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. Vital signs measurement and electrocardiogram (ECG) assessment text was updated to clarify patient positioning during the assessments. 4. 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. 5. Fazirsiran supply, preparation, storage, and labelling information was updated, and includes guidance on allowing the fazirsiran vial to come to room temperature before administration. 6. The risks assessment section (Section 4.8) was restructured to be consistent with information in the current Investigator's Brochure (subheadings were added and the order of paragraphs was changed). 7. Exploratory endpoints (Section 5.4) were updated to be consistent with the exploratory endpoint described in the protocol synopsis. 8. A pre-specified subgroup analysis (analysis based on liver co-morbid condition) was removed because it was similar to another pre-specified subgroup analysis. 9. Text was revised to make administrative updates, correct grammatical and formatting errors and inconsistencies, update abbreviations, update references, and update text
29 August 2022	(continued) 1. Text was updated to explain that the interim analysis has been completed and a fazirsiran dose was selected for the open-label phase. All subjects who are ongoing after dose selection will receive the selected fazirsiran dose (200 mg) in the open-label phase for the duration of the study. 2. Pulmonary function test text was updated to clarify instructions for performing spirometry and DLCO. 3. A pre-specified subgroup analysis (analysis based on liver co-morbid condition) was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported